JOURNAL OF THE
American Geriatrics Society
*Official Journal of the*
*American Geriatrics Society · American Therapeutic Society · Texas Geriatrics Society*

VOLUME V *October, 1957* NUMBER 10

# OBSERVATIONS ON THE MANAGEMENT OF HYPERTENSION, INCLUDING THE USE OF ANTIHYPERTENSIVE DRUGS

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Introduction of new antihypertensive agents and re-evaluation of some of the older ones have greatly enhanced the physician's ability to maintain his hypertensive patient's blood pressure at any selected level. At the same time, it is becoming increasingly evident that hypertension may be caused by a variety of unrelated factors, and technics for determining many of these underlying causes have likewise improved. More than ever, therefore, it is becoming the responsibility of the physician to search diligently for the primary cause of the hypertension and to attempt appraisal of the various factors involved, before deciding which method of treatment or which antihypertensive agent best meets the physiologic demands of the particular patient involved. Having selected a therapeutic regimen, the physician must adjust it meticulously in order to attain a specific result and must avoid the temptation to offer an inadequate regimen as a placebo to both himself and the patient.

We (1) recently reported the results obtained with chemotherapeutic agents in the treatment of 81 hypertensive patients during a period of six years. We should now like to give our opinion of the value of each of the antihypertensive drugs used, and to cite certain examples in which their use is clearly not indicated.

## METHODS

The method of study was described in our previous report (1). In addition to a complete history and physical examination, the renal and cardiac statuses of each patient were investigated by means of electrocardiography, roentgenography of the chest, excretory urography, urea clearance and other pertinent tests. For a period of two weeks, blood pressure was determined four times a day either in the hospital or at home (the patient was taught to take and record his own blood pressure). These readings served as a base line for evaluation of the therapeutic response and as a guide for helping to select the type of treatment. In addition, aortography was carried out in patients less than 25 years of age, as well as in those more than 50 years old whose hypertension was of short duration. The presence of a pheochromocytoma was excluded. Sodium, potassium, chloride

and $CO_2$ determinations were obtained routinely, to help exclude the diagnosis of primary aldosteronism.

If ganglionic blocking agents, alone or in combination with other drugs, were considered to be the treatment of choice, the patient was admitted to the hospital for regulation of dosage and determination of the appropriate time at which the medication should be given. This involved charting the blood pressure every hour with the patient in the supine, sitting and standing positions, respectively, while awake. If ganglionic agents were not to be employed, the patients were treated on an out-patient basis. All were closely followed by means of periodic examinations and by blood pressure records, which the patients were instructed to mail to us monthly or weekly, as required, so that the dosage could be appropriately adjusted.

## MEDICAL MANAGEMENT OF HYPERTENSION

The preferred medical management of *malignant hypertension* is use of a ganglionic blocking agent combined with reserpine (Serpasil®) or another rauwolfia derivative. In the patients whose blood urea nitrogen concentration was less than 40 mg. per 100 ml. the malignant process was "reversed," and all were able to resume their previous occupation. All those whose blood urea nitrogen level was more than 40 mg. per 100 ml. died within ten months of institution of treatment. There was no good correlation between adequacy of the blood pressure response and symptomatic improvement, although both systolic and diastolic pressures were significantly lowered in all patients. Patients with *grade III hypertension* (2) were treated in the same manner.

Those with *grade II hypertension* (2) presented a more difficult problem from the standpoint of evaluation of the need for, and response to treatment. It was almost impossible to prove that life has been prolonged, and actually the best manometric response might be associated with the earliest demise. The decision as to which patients with grade II hypertension should be treated, and how vigorous should be the attempt to control their hypertension, presents a therapeutic dilemma. Although essential hypertension is relatively benign, periodic observation of such patients is imperative in order to detect changes when they occur and to institute appropriate therapy promptly.

We advise vigorous treatment only for patients whose diastolic pressures are grossly elevated and for those with evidence of advancing vascular disease (increase in size of the heart, electrocardiographic changes, or sudden elevation of diastolic pressure). There are two reasons for this. First, essential hypertension is a relatively benign disease. Secondly, the expense of a therapeutic regimen that may have to be continued for twenty or more years must be kept in mind. We always try the simplest regimen and the least expensive drugs first. Yet the argument against this rather facile philosophy is worthy of consideration. In most patients with essential hypertension (arteriolosclerosis) death is due not to the hypertension itself, but to the development of a strategically located atherosclerotic plaque that ultimately obstructs coronary or cerebral circulation. If the still unproved but generally accepted theory that hypertension predisposes to, or hastens development of atherosclerosis be correct, it would seem prudent to

treat the hypertension as soon as it is detected rather than wait for development of its untreatable sequela (atherosclerosis). This dilemma will be resolved when the relationship between hypertension and atherosclerosis is firmly established or, alternatively, it can be conclusively demonstrated that vigorous treatment of patients with early benign hypertension postpones the onset of atherosclerosis and prolongs life.

### IMPRESSION OF THE RELATIVE MERITS OF ANTIHYPERTENSIVE DRUGS

1. *Hydralazine* has proved too toxic for routine treatment of high blood pressure.

2. *Veratrum*. The effective and the toxic oral doses of Veralba,® the drug with which we have had most experience, are almost identical. The typical "feeling" in the throat and vomiting are usually present by the time a significant drop in blood pressure is noted. Therefore, we do not consider this drug to be of much value when given orally. Its value, when given intravenously, is illustrated by the following case:

*D. D.*, a white girl, 13 years old, was first seen at the Ochsner Clinic in 1952 at the age of 11 years. Exhaustive studies resulted in a diagnosis of chronic pyelonephritis, for which she received large doses of Aureomycin® for six weeks. In February 1953 mild albuminuria was present. The blood pressure was 130 mm. Hg systolic, and 80 mm. diastolic. The patient moved to Connecticut, where results of studies undertaken in August 1953 were reported as "negative"; she later returned to the south.

On March 1, 1954, severe headache, hematuria and convulsions suddenly developed. The next day the child, in deep coma, was admitted to the Ochsner Foundation Hospital. She had no further convulsions but she remained comatose for the next ten days. The blood pressure on admission was 182 mm. Hg systolic and 142 mm. diastolic; during hospitalization it rose as high as 230 mm. systolic and 180 mm. diastolic. The ocular fundi appeared normal; there was no papilledema. The heart and lungs were normal, and there was no edema. Gross hematuria and severe albuminuria were present, but the blood urea nitrogen concentration remained normal. Results of the Regitine® test, perirenal air insufflation, aortography, excretory urography and muscle biopsy were normal.

Continuous intravenous drip of Veralba in a 5 per cent solution of glucose in distilled water for ten days adequately controlled the blood pressure. The urine became normal after five days and remained normal throughout the remainder of hospitalization. The patient became rational by the seventeenth hospital day. Thereafter, she steadily improved and was discharged four weeks after admission.

In April 1954 the blood pressure was 135 mm. Hg systolic and 100 mm. diastolic. Results of laboratory studies were within normal limits. Figure 1 illustrates the response of the blood pressure to intravenous administration of Veralba.

3. *Rauwolfia*. Both the combination of alkaloids (Raudixin®) and Serpasil® have been used by us. Results with the double-blind technic were not striking but, when the blood pressure during Serpasil therapy was plotted against the pressure when a placebo was administered, we were able to select the periods during which Serpasil was given in 3 out of 4 cases. The mildly agitated patient is definitely helped. These preparations can be a useful weapon if employed intelligently. We consider rauwolfia preparations to be more than placebos, but usually they are incapable of greatly lowering the blood pressure. Patients who have previously had thoracolumbar sympathectomies are important exceptions

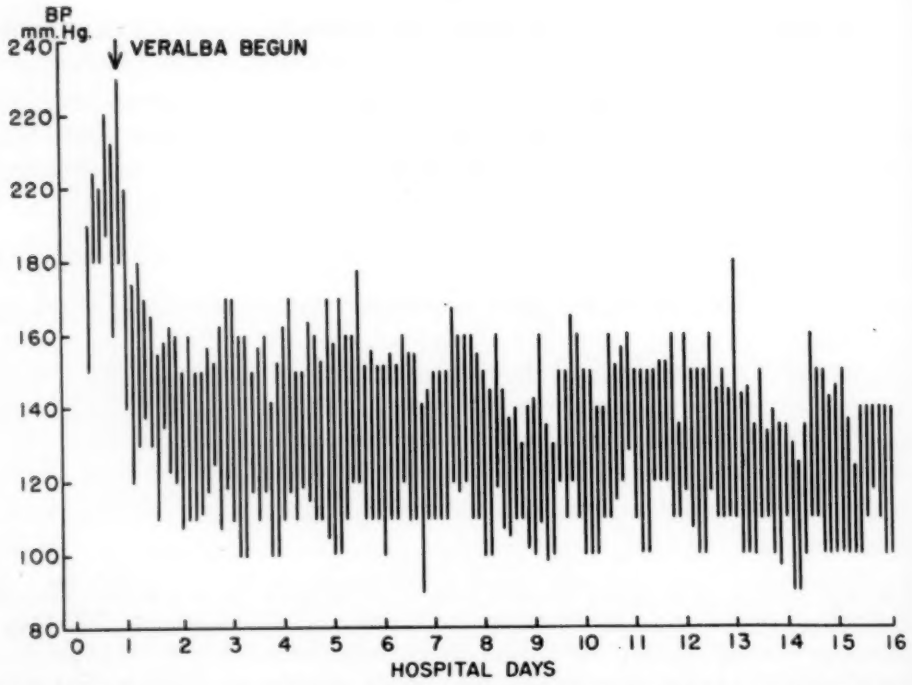


FIG. 1. Blood pressure readings of D. D., aged 13 years, just before and during intravenous administration of a solution of 900 cc. of 5 per cent glucose in water containing 0.004 mg. per cc. of Veralba at the rate of 4 to 10 drops a minute.

to this generalization. In some of these patients, 0.05 mg. of Serpasil three times a day can produce severe orthostatic hypotension.

Nasal stuffiness and depression are the chief untoward reactions observed with the use of rauwolfia preparations. In several patients we noted that depressive symptoms could be produced or alleviated almost at will by starting or discontinuing this drug.

4. *Ganglionic blocking agents*, in combination with reserpine, have proved to be the most valuable drugs in the management of severe essential or malignant hypertension. The pioneer drug in this field, hexamethonium, has been largely replaced by newer drugs, which in our experience have offered no more certain or consistent control of the blood pressure. However, approximately as good manometric control has been obtained, in association with a much simpler and more convenient schedule for the patient. We have noted no more predictable or smoother response to mecamylamine (Inversine®) than to either pentolinium (Ansolysen®) or chlorisondamine (Ecolid®), although supposedly Inversine is completely absorbed from the gastro-intestinal tract. Unpredictability of response to a given dose of a ganglionic blocking agent must be due to factors other than irregular absorption from the gastro-intestinal tract.

### HYPERTENSION IN THE YOUNG

In the younger age group essential hypertension is extremely rare. This diagnosis should never be entertained until all other possible causes of hypertension

have been rigorously excluded. Most often, primary renal disease (either pyelonephritis or glomerulonephritis) or a congenital abnormality of the renal artery will be discovered. The following case illustrates the diagnostic and therapeutic difficulties that may be encountered:

*W. F.*, a white man, aged 23 years, came to the Ochsner Clinic because of severe sustained hypertension of one year's duration, associated with severe headaches, nausea, vomiting and sweating. Results of examination elsewhere (including Regitine tests) were normal except for reduplication of the right kidney. Treatment with Ansolysen had been unsuccessful.

On admission, the blood pressure was 230 mm. Hg systolic and 150 mm. diastolic (brachial) with the patient recumbent; 220 mm. systolic and 170 mm. diastolic, (brachial) with the patient standing; and 270 mm. systolic in the legs, with the patient supine. Severe sclerosis of the retinal arterioles and arterio-venous nicking were noted. The heart was overactive.

Results of laboratory studies, which included a complete blood count, sedimentation rate, glucose tolerance test, blood urea nitrogen concentration, urea clearance, serum cholesterol and total protein levels, albumin-globulin ratio, $CO_2$ capacity, serum concen-

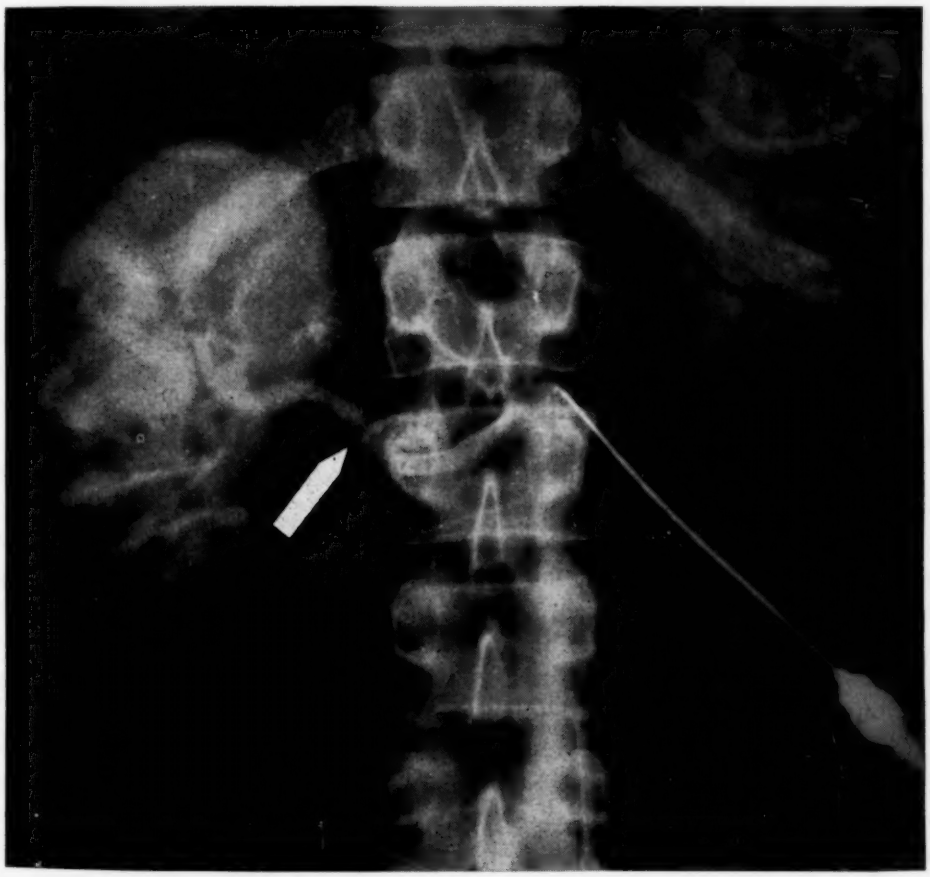

FIG. 2. Aortogram of W. F., aged 23, in which constriction in the midportion of the right renal artery (arrow) is demonstrated. Left renal artery is not seen but was normal in other views.

trations of chlorides, sodium and potassium, examination of feces, serologic tests for syphilis and basal metabolic rate, were all within normal limits. Low voltage of the T waves in leads I and $V_5$ and $V_6$ was noted in the electrocardiogram. A Regitine test yielded negative results.

No abnormality was detected in the roentgenogram of the chest. Reduplication of the right kidney was noted in the excretory urograms. A narrow band-like constriction in the midportion of the right renal artery was seen in the aortogram (Fig. 2). The left renal artery appeared normal.

Upon surgical exploration of the right renal region, a constriction was found in the midportion of the right renal artery. The intra-arterial pressure was 190 mm. Hg in the normal proximal segment and 80 mm. in the distal segment. The constricted area was resected and end-to-end anastomosis was accomplished. The final pathologic diagnosis of the resected segment was intimal and medial arteriosclerosis.

Immediately after operation there was a significant reduction in the blood pressure. Considerable improvement in the patient's condition was noted, and two months later the blood pressure was normal.

We (3) previously reported the case of a girl 16 years old whose hypertension was cured by surgical removal of a kidney that was the seat of both pyelonephrosis and an abnormality of uric acid excretion.

### HYPERTENSION IN THE AGED

Reflection on the physiologic mechanism by which blood pressure is normally maintained will explain most of the cases of hypertension in the aged. Blood pressure is maintained by several factors working in combination with each other. The heart discharges a given quantity of blood into the aorta in a unit period of time. The arterial system is always full, so that the sudden ejection of blood by the systolic contraction of the heart overfills the great vessels and the arterial walls stretch. Pressure rises in the arterial system until the velocity of flow through the most distal portion, the arterioles, is great enough to balance the inflow. Because the surface area of the arteriolar system is much greater than that of the larger vessels, the former has much more friction resistance. It is probable that spasm or narrowing of the arteriolar system, whatever the cause, with resulting increase in peripheral resistance, is the prime factor in elevation of the diastolic blood pressure. The diastolic pressure represents the constant load that arterial walls have to carry. Arteriolar disease or spasm will increase this load by reducing the amount of flow through the smaller vessels in a given time and thereby increasing the blood load in the arterial system.

The factor concerned chiefly with maintenance of diastolic pressure is elasticity of the vessel wall. At completion of systole, the overstretched elastic walls rebound and return the arterial lumen to its previous diameter, thus driving the blood forward in a continuous stream between the heart beats. If this did not occur, arterial pressure would fall to zero after each systole. Any reduction in elasticity, other factors remaining unchanged, will tend toward lowering of the diastolic pressure. Sclerotic changes decrease the elasticity of the aorta and larger arteries, so that they will not so readily accommodate blood ejected during systole.

Thus, as the elasticity of the arteries diminishes, there is normally a rise in the systolic pressure with a normal or slightly lower than normal diastolic pressure. If it requires the dignity of a name, this should be called arteriosclerotic hypertension. It should always be remembered that it bears no relation to essential hypertension and requires no specific therapy. Some elderly patients have elevation of both the diastolic and systolic blood pressures. If the diastolic pressure returns to normal after rest in bed for forty-eight hours, we classify the condition as arteriosclerotic hypertension. The transient elevation of the diastolic pressure is presumably due to an increase in cardiac output because of effort or anxiety, which is no longer so easily compensated for by pressoreceptors in the carotid sinus and aortic arch. The only treatment indicated is mild sedation, designed to lessen anxiety and lower the cardiac output. Use of ganglionic blocking drugs not only would be unphysiologic but would constitute a grave threat to the patient's life by seriously compromising his coronary or cerebral circulation or even both. Furthermore, it should be borne in mind that each of the newer antihypertensive agents bears its own price tag. With the derivatives of rauwolfia it is the stuffy nose, the occasional nightmare, depression, or even signs of parkinsonism. With the veratrum derivatives it is chronic nausea, threatening to culminate in projectile vomiting at some unpredictable and particularly embarrassing moment. With hydralazine it is the flush, headache, or even generalized arthralgia. With the ganglionic blocking agents in combination with one of the newer drugs it is giddiness on standing, distended abdomen, blurred vision, constipation, and further difficulty in emptying what may already be a sluggish and recalcitrant bladder. Unfortunately, the effect of the drug is either complete block of transmission at the ganglion or none at all; to be effective it must block completely and the price for this "blockade" is more "parasympathetic" than "sympathetic." And, finally, $30 to $60 paid monthly to the pharmacist may penetrate deeply into a small annuity. Therefore these drugs, important as they are when truly indicated, have no place in the management of the systolic hypertension that is but the reflection of decreased elasticity of the larger arteries. This is better controlled with mild sedation, which serves to keep the cardiac output more nearly basal.

As in the child, if one discovers truly fixed diastolic hypertension in an elderly patient, every attempt must be made to discover a primary cause. Renal disease can easily be differentiated. Pheochromocytomas may be observed in patients of all ages. Our oldest patient was 72 years of age at the time a pheochromocytoma was surgically removed. Since the renal vascular bed is disproportionately large, one would expect infarcts of the kidney at least to rival those of the myocardium or cerebrum and to be a common cause of diastolic hypertension in the aged. We search constantly but rarely do we find one. Possibly aortography and differential urinalysis are methods too crude to detect a small but important renal infarct, and a history of pain in the abdomen or flank associated with gross hematuria is rare indeed.

More common is demonstration of a plaque partially obstructing one or both renal arteries. Illustrative of this is the following case:

*G. F.* was a white man aged 69, in whom hypertension was first discovered ten years before we saw him. The hypertension had always been of a mild fluctuating character until nine months before admission to Ochsner Foundation Hospital, when he had sustained a fractured vertebra in an automobile accident, associated with severe pain in the left lumbar region, albuminuria, and hematuria. Since that time the hypertension had been severe and persistent. Three years prior to admission the patient had a thrombus or embolus in the left leg. Four months prior to admission acute attacks of left ventricular failure were controlled by digitalization. The blood pressure responded unsatisfactorily to ganglionic blocking agents.

On admission the patient was mentally confused. The blood pressure was 240 mm. Hg systolic and 120 mm. diastolic with the patient in the recumbent position, and 148 mm. systolic and 120 mm. diastolic in the standing position. The ocular fundi showed only grade II sclerosis. The chest was emphysematous, and the heart sounds were distant. The liver was palpable on deep inspiration. Peripheral pulsations were all decreased.

Results of routine laboratory studies were within normal limits. Slight cardiac enlargement and calcification in the aortic notch were demonstrable roentgenographically. Typical evidence of left ventricular strain could be seen in the electrocardiogram. In the excretory and retrograde urograms, poor function of the right kidney was suggested. Differential urinary studies could not be obtained.

Aortography was carried out because of the possibility of either an arteriosclerotic plaque in the right renal artery or an infarct of the right kidney. In the aortogram, irregularities were noted in the right side of the aorta in the region of the right renal artery, and an irregular appearance of the right renal artery consistent with an atherosclerotic plaque (Fig. 3).

Right nephrectomy was well tolerated, but postoperatively there was no remarkable reduction in the level of the blood pressure. It again became necessary to control the blood pressure with ganglionic agents before discharge from the hospital. Pathologic study of the right kidney revealed chronic pyelonephritis with severe nephrosclerosis.

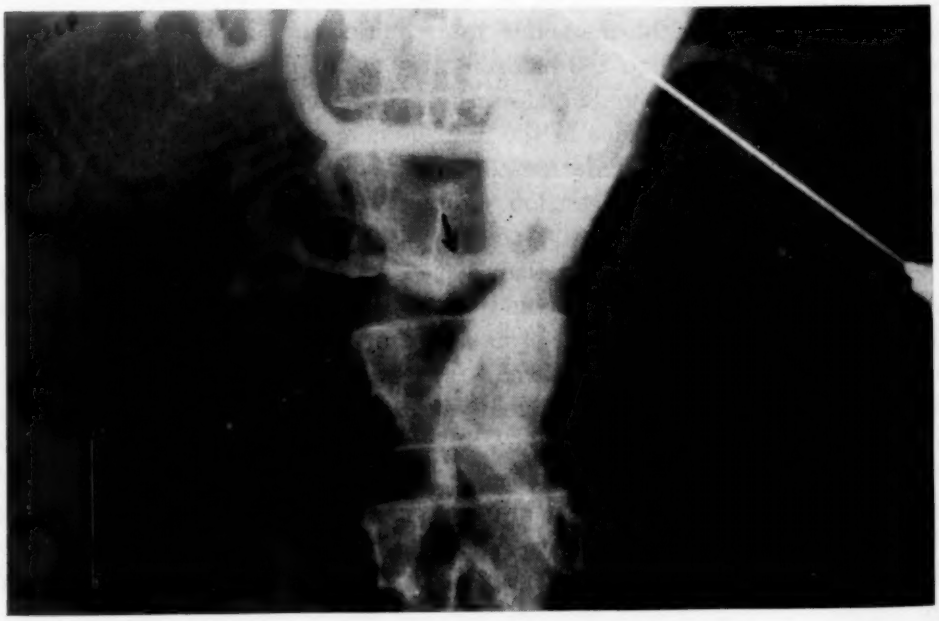

FIG. 3. Aortogram of G. F., aged 69, in which a normal left renal artery and irregular narrowed right renal artery (arrow) are demonstrated.

The therapeutic dilemma is real. Nephrectomy, endarterectomy or even a bypass shunt might prove curative if performed shortly after the hypertension is discovered. Yet, as in the case just presented, the arteriosclerosis may be so widespread that too little could be accomplished to justify the risk. The assumption that there might be similar plaques in either the coronary or cerebral vessels makes treatment with ganglionic blocking agents hazardous. One should be guided by the patient's age (if comparatively young, surgical intervention is the logical approach) and by one's impression of the severity of the hypertension as compared with the severity of the arteriosclerosis. Each patient becomes a law unto himself and should be treated according to the physician's best judgment.

## SUMMARY AND CONCLUSIONS

1. Results of the use of chemotherapeutic agents (hexamethonium, hydralazine, mecamylamine, pentolinium, chlorisondamine veratrum, rauwolfia derivatives) in the treatment of hypertension have been presented, in an effort to evaluate their usefulness.

2. All patients with malignant hypertension or severe essential hypertension should be hospitalized for careful regulation of the blood pressure by administration of a combination of a ganglionic blocking agent and reserpine. These patients should be taught to take their blood pressure readings at home, and to regulate the dosage of the ganglionic blocking agent by means of a sliding scale, depending on the level of the blood pressure at intervals which are regulated according to the particular agent being used.

3. If renal function is good, and the blood urea nitrogen concentration is below 40 mg. per 100 cc., most patients with malignant hypertension can be assured that their blood pressure can be controlled and the course of the disease "reversed."

4. Selection of a drug for treatment of mild or moderate essential hypertension must be highly individualized. The simplest and least expensive drug should always be tried first. Hydralazine has been practically abandoned by us because it is more toxic than reserpine and otherwise seems to have little advantage over that preparation. Because the therapeutic and toxic levels of veratrum are almost identical, this drug is rarely considered to be of use.

5. The rauwolfia derivatives have effects that are greater than those of a placebo or a mild sedative, but unpredictable. These preparations are potent antihypertensive agents in patients who have previously had bilateral lumbodorsal sympathectomy, and must be given cautiously and in small doses initially.

6. As ganglionic blocking agents, chlorisondamine and mecamylamine enjoy the advantage over hexamethonium and pentolinium that the regimen is simpler for the patient, since he is required to take his blood pressure and medication less often.

7. Inversine seems no more predictable or uniform in its action than Ecolid. Since it is evidently completely absorbed from the gastro-intestinal tract, unpredictability after its use must be due to factors other than absorption.

8. Because essential hypertension is rare in both the young and the elderly

patient, every effort should be made to detect a primary cause (renal disease, aneurysm or constriction of one or both renal arteries) in these two age groups.

9. The fluctuating and principally systolic hypertension of elderly patients is not generically related to essential hypertension and requires no treatment other than mild sedation to decrease the fluctuations in the cardiac output.

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# REALISM IN THE USE OF TRANQUILIZING DRUGS

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"Those friends thou hast, and their adoption tried,
Grapple them to thy soul with hoops of steel;
But do not dull thy palm with entertainment
Of each new-hatch'd unfledg'd comrade."

Polonius in Hamlet (Shakespeare)

Psychosomatic medicine is now a respected member of the medical specialties. The general public is also aware of its presence and importance. Bodily ills of speculative etiology, including such diverse complaints as hypertension, obesity and skin disorders, are classified as psychomatic or neurogenic. With this recent setting, it is little wonder that the "tranquilizing," "calming" or "ataraxic" drugs have received such an enthusiastic welcome and abundant use. Anxiety and the need to avoid it are thought by many to control behavior. The tranquilizing drugs presume to control behavior by controlling anxiety.

Sedative drugs are defined as pharmacologic agents which will quiet overstimulation of the central nervous system without drowsiness—agents which quiet activity (1). The bromides, chloral hydrate and the long-acting barbiturates have always been classified as such when proper dosage and pharmacologic action are carefully considered. Tranquilizing drugs are also sedatives in proper dosage but it has been assumed that they have a quieting effect above and beyond this. Literature, both published and advertising, frequently suggests that these drugs can "normalize" both anxiety and depression. It would be a great advance for mankind if a drug were able to overcome the neurotic drives which lead us to unhappiness. Unfortunately the facts, when carefully considered, leave little hope that such a drug has been found. It is possible that we are dealing with semantics rather than facts. It appears that these new drugs simply add to our list of available sedatives. Some, such as chlorpromazine, have activity in other therapeutic areas and will be considered later. Each must have limited but definite indications, which in some instances are still unclear. The older drugs which have stood the test of time as for usefulness, and are well known for their side-effects, need not be abandoned in the enthusiasm for a catch-phrase. It is our need and purpose at the present time to attempt a realistic evaluation of the newer drugs. Some will take their proper place among the recognized time-tested sedatives. Others will disappear for lack of fulfillment of purpose or because of untoward toxicity, as the first wave of enthusiasm subsides. It would be unfortunate, however, if a potentially valuable drug be abandoned because expectation of its value has been exaggerated and a true outline of its usefulness not properly presented.

## CHLORPROMAZINE

The significant pharmacologic action of chlorpromazine is its antagonism to naturally occurring neurohumoral substances (2). It is somewhat antagonistic to

histamine, acetylcholine, noradrenaline and cholinesterase; and it is a powerful antagonist of adrenaline and counteracts the activity of serotonin (5-hydroxytryptamine). It prevents shock produced experimentally in animals, reduces oxygen consumption when added to a slice of brain in a Warburg flask, and blocks out some conditioned reflexes. In addition to its antagonism to neurohumoral substances at the periphery, it has central effects, probably at the hypothalamus. Little is known of its central mode of action.

Anxiety may be induced experimentally by infusing epinephrine in amounts too small to evoke gross somatic changes (3). Anxiety occurs in hypoglycemia and there is a relationship between it and epinephrine. The concept that anxiety is related to an excess of epinephrine or sympathotonia is attractive as an explanation of the emotional effect of chlorpromazine through its adrenolytic action.

The clinical uses of chlorpromazine are legion (4) and its extreme usefulness for specific acute conditions is without equal. It is of limited value for the neurotic patient, aside from its potential toxicity. It has a real if limited place in the treatment of some chronic psychotic states if therapy can be maintained for long periods at high dosage levels. In view of the toxic effects, such as jaundice, occurring after prolonged administration, the use of chlorpromazine should be limited to acute otherwise refractory disease states or severe psychoses.

### RAUWOLFIA SERPENTINA

Reserpine causes the release of 5-hydroxytryptamine (serotonin) from the bound state in animal tissues, including brain (5). Experimental devices have not yet determined whether 1) sedation is due to the release of serotonin which acts as a sedative, or 2) serotonin is a stimulant which upon release from brain tissue and immediate destruction by amino-oxidase, causes sedation.

In man as well as the laboratory animal, the heart rate is slowed, blood pressure is lowered, intestinal movements are increased and sedation is effected with large doses of Rauwolfia (6); but it is labile hypertension which is decreased and labile tachycardia which is diminished. Clinical usage suggests that it is valuable in patients with autonomic nervous system imbalance, predominantly sympathotonia (7).

Its value in severe chronic psychosis, as that of chlorpromazine, cannot be minimized (8). These two substances have changed the overall management of patients in mental institutions. In the treatment of these very sick patients, large effective doses are utilized and the side-effects can hardly contraindicate the use of these drugs.

Anxious patients with tachycardia, labile hypertension and vasomotor instability usually respond well to Rauwolfia drugs. One should remember the property of delayed onset of activity and also the persistence of activity following discontinuance. It appears that when an effect is achieved, the maintenance dosage may be markedly reduced. Dosage requirement is an individual matter. Some anxious patients will respond to as little as 25 mg. of whole root per day, whereas others require much larger doses. This variation seems not to be a matter of weight, but rather of individual response (7). The need for careful dosage and

observation of the therapeutic effects and side-reactions is obvious. When properly applied and carefully regulated, Rauwolfia drugs and their alkaloids are relatively safe and most efficacious in both neurotic anxiety with autonomic lability and chronic psychoses.

### PROMAZINE

This drug is closely related chemically to chlorpromazine. Early experimental work indicates that it is antagonistic to neurohumoral substances but far less so than chlorpromazine. Studies in psychotic patients in mental hospitals indicate that it has a pronounced quieting effect. There have been no indications of side-effects or toxicity simulating those of chlorpromazine. The chemical formula suggests that this may be so.

It has a quieting effect in anxious patients but its soporific dose is close to the sedative dose. The subjects are quieter, but are also sleepy. It is possible that further experience may determine a dose which will offer adequate sedation without hypnosis.

### OTHER DRUGS

Within the past year other drugs with "tranquilizing" properties have been introduced. Meprobromate and hydroxyzine hydrochloride are available in this country, and benactyzine hydrochloride in Denmark and England. They are suggested for treatment of the mildly neurotic patient who has good insight and is aware of the stress which causes symptoms. However, awareness of the situation and good insight are fundamental in the self-evaluation of tension, and this evaluation often causes the tension and its somatic components to disappear. Drugs for which such claims are made must therefore be measured with extreme care, for results attributed to the drug may be the result of the patient's own emotional efforts. Pharmacologic activity is difficult to demonstrate, and controlled clinical studies are not yet available. We may expect that within a short time these drugs will be relegated to their proper position in therapeutics.

### DISCUSSION

Drugs which influence emotions have been available for centuries and in all lands. Alcohol, tobacco, betel nut, cocoa leaf, opium and heroin are well known examples. Restraint in their consumption is extremely difficult and habit or addiction is rapidly established. Excessive usage of such substances frequently leads to devastating end-results. These drugs which act perceptibly on the emotional content have serious and often harmful effects on organic structures and emotional patterns. It is difficult to contemplate a substance causing emotional changes without the danger of habit formation, addiction, toxicity or organic effects.

Nervous tension and its somatic reactions such as palpitation, hyperventilation, headaches, chest pain and other subjective manifestations are frequent accompaniments of our complicated existence. With most of us, these tensions come and go as anxieties develop, and we evaluate them realistically. Tension

experienced in anticipation of a real situation such as acting, public speaking or taking an examination is frequently dispelled as soon as the individual enters into the exercise of the task. It is therefore extremely difficult to evaluate clinically a drug which is presumed to act rapidly and with sustained effect in situations productive of anxiety or tension. Well controlled convincing studies are lacking, except for those pertaining to chlorpromazine and Rauwolfia, which have important and measurable pharmacologic activity.

Tension and anxiety are not only products of progress; they are also factors in its development. Anxiety creates the drives that lead us to progress. Tranquilizing drugs of the past (including betel nut, narcotics and alcohol) have moderated drives, altered physical structure and destroyed emotional patterns. In this sense they have impeded progress. It is not pleasant to live with constant anxiety. There are, however, real situations which are productive of anxiety and which anxiety and its attendant drives serve to master. To destroy these anxieties may destroy our mechanism for handling these situations.

This era of organic chemistry in medicine has created extremely valuable drugs. It has also allowed laxity in diagnosis and the use of other therapeutic devices. The role of the physician cannot be replaced with drugs. Drugs can only be useful when the physician has established the role of friend, helper and true mediator, and then prescribes with full knowledge of the drug and the patient.

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# TREATMENT OF ANXIETY AND AGITATION WITH PROCLORPERAZINE IN GERIATRIC PATIENTS

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This paper describes the effects of proclorperazine[1] upon geriatric patients suffering in varying degrees from emotional disturbances, chiefly anxiety and agitation. The effects of the drug upon nausea and vomiting are also considered.

Proclorperazine, a recently-introduced tranquilizer and antiemetic, is a member of the phenothiazine family of compounds. According to the available pharmacologic data (1, 2), proclorperazine is two to six times as potent as chlorpromazine in combating apomorphine-induced emesis in dogs. In rats, the drug effectively inhibits the conditioned escape response, and this inhibition appears to be a measure of the ability of a drug to act as a tranquilizer. The $L_D50$[2] for mice is about 1080 mg. per Kg. of body weight (the $L_D50$ of chlorpromazine is about 350 mg. per Kg.), indicating that proclorperazine is relatively safe. Used in extremely large doses in human beings, it has sometimes produced one or more of the following: lethargy, somnolence, moderate hypotension, and mild extrapyramidal symptoms (tremor, salivation, speech impairment, numbness, and spasm of the voluntary muscles). All of these manifestations, however, disappeared within twenty-four hours after the drug was withdrawn.

In preliminary clinical studies (3, 4) of proclorperazine in neurotic patients typical of those so commonly found in general practice, 59.1 per cent exhibited complete relief of mental and emotional disturbances (including psychosomatic disorders) and 37.5 per cent, moderate to marked relief. Laboratory data showed no hepatic, renal or hematopoietic changes.

## METHOD

Seventy patients (40 females and 30 males) ranging in age from 60 to 94 years were given proclorperazine for fourteen to sixteen weeks. Of these, 47 were inpatients under strict surveillance at the Forest Hills Nursing and Rehabilitation Center, and 23 were ambulatory patients seen in private practice.

Among the 47 inpatients, 23 were severely agitated, bordering on being psychotic. The remaining 24 were patients with mild to moderate senile agitation, including some with senile anxiety-depression and agitation associated with terminal carcinoma. Eight of these suffered severe pain and vomiting. All of the inpatients manifested wide degrees of hypermotoricity, anxiety (with or without concomitant somatic disease), depression, hostility, aggressiveness and occasionally assaultiveness. Organically, the 47 inpatients suffered from one or more of these ailments: arteriosclerosis, cardiovascular disease, stroke, cancer, osteoarthritis, Parkinson's disease, diabetes, peripheral vascular disease, and various nutritional disturbances. They had been placed under custodial care because of their families' inability to cope with their behavior.

All of the ambulatory patients seen in private practice were moderately agitated due to inadequate emotional adjustment engrafted on some physical disability. They exhibited

[1] Supplied as Compazine by Smith, Kline & French Laboratories, Philadelphia, Pa.

[2] Dose which is lethal for 50 per cent of the test objects.

varying degrees of fears, phobias, obsessive-compulsive reactions, anxiety, and conversion hysterias. There were related physical ailments in every case, including hypertensive cardiovascular disease, diabetes mellitus, gastro-intestinal disease, and osteoarthritis.

An initial oral dosage of 5 mg. of proclorperazine three or four times daily was given to emotionally disturbed patients following a week or more during which no other aliphatic sedatives or tranquilizers were used. The dosage was increased to 10 mg. three times daily (but never more than this) when the response was inadequate after a week. In patients who refused oral medication, or who were vomiting for one reason or another, proclorperazine was administered intramuscularly in aqueous solution. Again, the initial dose was 5 mg. or, when greater effectiveness was desired, 10 mg., three times daily.

Laboratory studies were performed on every subject prior to initiation of therapy with proclorperazine and, when possible, every three weeks during continuous therapy in order to detect early signs of toxicity. These studies included complete blood counts and determinations of sedimentation rate, cephalin flocculation, alkaline phosphatase, and serum bilirubin levels.

At weekly intervals, complete physical examinations were made in conjunction with patient interviews and discussions with the charge nurses on the different shifts. Families of ambulatory patients were questioned to determine changes in attitude and behavior. A predetermined series of key personality elements (Table 1) was utilized to aid in the evaluation of the patients' mental and emotional progress.

The difficulty involved in subjecting agitated senile patients to any formal personality rating tests is obvious. However, by means of the simplified subjective tests which we created, for all practical purposes there was provided a basic medium for standardizing conduct reports from the various people involved in day-to-day observations.

At one period during the study, placebos were given by the single blind technique to 10 patients at the nursing home.

TABLE 1

*"Profile" Chart for Proclorperazine Treatment*

| Name: | Pretreatment Date: | Date: | Date: | Date: | Date: | Date: |
|---|---|---|---|---|---|---|
| Anger | | | | | | |
| Anxiety (fear) | | | | | | |
| Assaultiveness | | | | | | |
| Depression | | | | | | |
| Destructiveness | | | | | | |
| Dishonesty | | | | | | |
| Envy | | | | | | |
| Judgment defect | | | | | | |
| Memory defect | | | | | | |
| Restlessness | | | | | | |
| Tension (tremor) | | | | | | |
| Eating habits | | | | | | |
| Sleeping habits | | | | | | |
| Interpersonal relations | | | | | | |
| Recreative abilities | | | | | | |
| Personal hygiene | | | | | | |
| Bowel habits | | | | | | |
| Nausea | | | | | | |
| Vomiting | | | | | | |
| Pain | | | | | | |

## RESULTS

Results with perclorperazine were classified as excellent, good or poor. Optimum improvement in interpersonal relationships with restoration of a measurable degree of equanimity and loss of agitation were the broad requirements for an "excellent" rating. Results were tabulated as "good" when the patient exhibited loss of anxiety and hypermotoricity, but occasionally reverted to the agitated state under conditions of mild stress. Anything less satisfactory than the foregoing was considered as a failure and listed as "poor."

Among the inpatients, who were mildly to moderately agitated, results were spectacular. Of the 24 patients, 22 (91.6 per cent) were benefited. There was an excellent effect in 8 and a good effect in 14. Among the latter 14 cases were 8 of abdominal malignancy with associated metastases.

The patients who reacted well became adjusted to the numerous phases of nursing-home routine. They engaged in occupational and recreational therapy more often, conversed without anger and hostility, obeyed the charge nurses, and took better care of their rooms and personal belongings. Restlessness and tension were reduced to a minimum. Acts of petty thievery, assaultiveness, and negativism no longer occurred after three or four days of therapy. Eating and sleeping habits improved. As a result of the general improvement, a large amount of annoying work for the staff was eliminated.

Of the 23 inpatients with *severe* agitation, only 13 (56.5 per cent) improved; in 4 the improvement was excellent, and in 9 it was good. Higher dosages of perclorperazine were not employed because of the manufacturer's preliminary cautionary statement that dosages in excess of 40 mg. a day would probably increase the incidence of side-reactions. Recent data (5), however, indicate that, with the proper precautions, proclorperazine can often be used efficaciously in dosages higher than those stated in this paper.

Among the 23 ambulatory patients, 19 (83 per cent) were benefited—with excellent results in 14, and good in 5. In only 4 cases (17 per cent) were the results poor. There was marked relief from pain, headache, vertigo and muscle spasm as well as measurable mitigation of the overall pattern of anxiety and agitation. Anginal attacks in the cardiac subjects were fewer and less severe. Control of diabetes improved. By reducing stress and tension, proclorperazine seemed to alleviate the accumulation of anxiety and symptoms secondary to emotional tension as well as those of organic origin.

Usually, the response to oral medication in all patients was manifest after two to three days, and attained an optimum level within a week. Thereafter, there was no diminution of effect after prolonged administration (four to sixteen weeks).

Proclorperazine by injection in 10-mg. doses three to four times daily controlled vomiting and psychic symptoms promptly. Among the 8 patients who had abdominal malignant conditions with associated metastases, 7 were afforded complete relief. In general the 5-mg. dosage was not as effective as the 10-mg. dosage.

### SIDE-EFFECTS

Mild side-effects appeared in 7 of the 70 patients. There was transient drowsiness in 4 patients, in 3 of whom it disappeared after the fourth day of treatment. The fourth patient was receiving 10 mg. three times daily and his tendency to sleep was overcome by reducing the dosage to 5 mg. three times daily. There were 2 instances of vertigo; one was in a 94-year-old man, and was relieved by reducing each dose from 10 mg. to 5 mg.; the other case was mild and transient. There was no evidence of dryness of the mouth, blurred vision, hypotension or bradycardia on either the 5-mg. or the 10-mg. dosage schedule. Transient pruritus, subsiding after the fourth day, was reported by one 70-year-old woman. She implicated a food to which she believed she was allergic.

One patient was accidently given 20 mg. three times daily through a misunderstanding by a member of the family. She reported that on the sixth day she noticed an inability to coordinate movements of the arms and legs. Fine motions of the fingers were particularly affected, and she felt that there was a generalized weakness in the leg muscles as well. Proclorperazine was withdrawn for three days, and complete subsidence of these extrapyramidal symptoms followed. On resumption of therapy with the 5-mg. tablet, none of these manifestations reappeared.

Repeated laboratory determinations did not reveal a single incident of physiologic disturbance among the 70 patients.

### DISCUSSION

In previous studies (6, 7) the author has pointed out the broad medical and sociologic implications involved in the care of the agitated senile patient. At present there are almost 15 million people in this country over 65 years of age, and the portent is that this number will increase to 20 million by 1975. It is certain that there will be at that time at least a proportionate increase in the number of agitated senile patients.

Earlier work with the tranquilizing drugs gave promise that appreciable inroads could be made into: relieving overburdened hospital facilities for more acute needs, distributing the present short supply of nursing personnel more effectively, and releasing many otherwise long-term hospital patients to home care to lead less troubled or even useful lives (7).

Although this promise has to a large extent been fulfilled, the side-reactions common to use of many of the earlier tranquilizers have placed some restrictions on the number of patients who can be cared for at home. This has been particularly true of geriatric patients, who traditionally are not only difficult to manage but are particularly susceptible to untoward reactions.

Proclorperazine, because it appears to be effective in alleviating the symptoms of anxiety, agitation and tension, and because it rarely produces side-effects—and usually of a transient, reversible nature—should serve to ease further the burden of caring for geriatric patients with mental and emotional problems.

## SUMMARY AND CONCLUSIONS

1. Proclorperazine was administered to 70 agitated geriatric patients, 47 of whom were under custodial care in a modern nursing home, and 23 of whom were in their homes. There was an overall effectiveness of 77 per cent.

2. Results were most outstanding in mild to moderately severe cases of senile agitation; 91.6 per cent of the patients in the institutional group and 83 per cent in the home group were benefited. Among the 23 nursing-home patients classified as having severe agitation bordering on psychosis, only 56.5 per cent showed improvement, with the dosages used.

3. The optimum dosage appears to be 5 to 10 mg., three or four times daily.

4. Symptomatic side-effects were mild in nature and were readily relieved in most cases by adjustment of the dosage. There was not a single case of toxicity affecting the hematopoietic, renal or hepatic systems.

5. In 1 instance of accidental overdosage, there was evidence of a mild extrapyramidal effect, notably muscular discoordination, which promptly disappeared on reduction of the dosage to the usual level.

6. Proclorperazine appears to be a safe and effective therapeutic agent for the relief of geriatric agitation, whether from a primary emotional source or secondary to somatic disease.

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# PRACTICAL CONSIDERATIONS IN THE MANAGEMENT OF THE GERIATRIC SURGICAL PATIENT

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Old man meets a young acquaintance after several months apart.

*Old man:* "It is certainly nice to see you. It's been at least six months since we have been together."

*Young man:* "It has been a long time. But what is six months in a lifetime?"

*Old man:* "Six months in a lifetime is not much in the middle, but is an awful lot at the end! . . ."

(After Dr. M. W. Durham)

## INTRODUCTION

The trend towards an ever-aging population has created medical problems, the nature of which can be appreciated best by a survey of the recent voluminous literature on this subject. There are numerous factors that may be attributed to the population shift toward the older age range, the most important being probably the increasing number of people who derive the benefits of modern advances in therapeutics and public health measures.

There are various articles in which the statistical aspects of this progressive lengthening of the life expectancy are analyzed (1–3). These features may be exemplified here by mentioning that whereas in 1900 only 1 person out of 25 in the United States was over 65 years of age, the ratio in 1955 was 1 in 12, and is expected to be 1 in 7 by 1975 (4). The medical implications of this situation are clear, as the physician is being called upon more and more to treat elderly patients (5). Similarly, with reference to the surgeon, the incidence of surgical disease in the old is disproportionately higher (6–12).

The purpose of this paper is to review some of the salient details in the management of this category of surgical patients.

## GENERAL CONSIDERATIONS

Ever since Nascher coined the word "geriatrics" at the beginning of this century (13), there has been a controversy concerning the precise age boundaries which such a term demarcates. It has been frequently emphasized that the ancient adage of a man being as old as his arteries is correct, for deterioration of the blood vessels has a profound effect on all homeostatic mechanisms. The cardiac, pulmonary, and renal reserves are decreased, and metabolism proceeds at a slower rate (14, 15). The appraisement of a patient's status should be based on physiologic age. The latter cannot be measured by the calendar. The significance of biologic age from the standpoint of surgery was recognized by Sir James Paget (16), who, almost eighty years ago, wrote:

"Years, indeed, taken alone are a very fallacious mode of reckoning age: it is not the time but the quantity of a man's past life that we have to reckon. . . . The old people that are

thin and dry and tough, clear-voiced and bright-eyed, with good stomachs and strong wills, muscular and active, are not bad; they bear all but the largest operations very well. But very bad are they, who, looking somewhat like these, are feeble and soft-skinned, with little pulses, bad appetites, and weak digestive powers; so that they cannot in an emergency be well nourished."

It is this latter group of individuals who present themselves most commonly for surgery. Although it is true that chronologic age and physiologic age rarely coincide, the spry, well-nourished, muscular, robust septuagenarian is infrequently encountered. Rather, one is confronted more often by a senescent patient who is handicapped by malnutrition, concurrent diseases, physical infirmities, and the stigmata of deteriorating metabolic and other systems (17). Marcus Seneca, the Roman stated many centuries ago that "Old age is a disease." The elderly person should still be thought of as a "brittle," effete patient, who is usually a poor surgical risk, and even more so when inadequately managed. Decreased mortality is commensurate primarily with competent surgical care.

A tenet of contemporary medicine is that no patient, regardless of age, should be denied surgery when such intervention may prolong life or reduce pain and disability (18–26). The traditional reluctance of surgeons to operate on the aged has given way to the realization that such surgery is no longer forbidding. Indeed, a vast array of major surgical operations are being performed in elderly persons with an ever-increasing degree of success (27–44). It may be generalized, therefore, and with justification, that surgery in the aged differs from that in younger individuals in details and degree of risk only (45–49). The basic concepts of operation are essentially unchanged. Because of the biologic quality of the material that the surgeon has to cope with, the problems of management are accentuated (50–61).

The timing and the type of surgical procedure are of paramount importance, and depend not only on the nature and extent of the disorder necessitating hospitalization, but also on the surgeon's clinical astuteness and judgment. Foldes (62) classifies operations into four groups according to the urgency entailed: (a) true emergency operations such as those for uncontrollable hemorrhage or embolus, (b) early operations, after initial corrective treatment, such as those for acute cholecystitis (63) or intestinal obstruction (64, 65), (c) necessary operations (no emergency) such as those for malignancy, and (d) elective operations, such as those for hernia. Only the last three types are under consideration here. In all cases the ideal goal of management is to convert an emergency procedure into an elective one, definitive surgery being carried out when the patient's condition is optimal (66). There have been reports that the mortality in geriatric emergency operations is two- to three-fold that in the geriatric elective type (66, 67). Contrariwise, it is obvious that temporizing at the wrong instant may be disastrous, and that deficits can be corrected only within the limits of time permitted by the seriousness of the surgical disorder (64, 68, 69).

More attention is being channeled in the direction of so-called "preventive surgery" (70, 71). It is self-evident, for example, that early repair of an uncomplicated hernia when it is discovered may obviate the necessity of dealing with

incarceration or strangulation of the bowel ten or twenty years later (65). This point of view was enunciated clearly in 1771 by Hill (72):

"Old men's diseases are hard to cure, but are easy to prevent. It must be a good natural fabric which has preserved itself so long; and the same strength may keep it much longer well, under good regulation."

## PREOPERATIVE CONSIDERATIONS

A deeper understanding of the metabolic changes consequent to operation, and the improved means of rapidly recognizing existing deficiencies have led to the establishment of better preoperative corrective measures. This step, of itself, has widened the margin of safety of many surgical procedures, and enhanced recovery while diminishing the development of untoward complications.

The importance of adequate preoperative management is reflected most strikingly in patients in whom the physiologic liabilities of advancing years make them incapable of withstanding acute stress unless suitably prepared. Modern surgery is hearkening to the Psalmist's plea:

> "Cast me not off in the time of old age;
> When my strength faileth, forsake me not."

Irrespective of the patient's seemingly wasted condition on admission, dramatic improvement can often be achieved by proper appraisal of existing reserves, promptly followed by the institution of appropriate replacement therapy for rectifying both previous deficits and current losses. The preoperative evaluation of the patient should include consultation and close cooperation between surgeon, internist, and anesthetist (25). Since the primary goal is treatment of the patient and not of the patient's chart, it is incumbent on the anesthetist to examine the former as well as the latter before deciding on the methods and admixtures of anesthetizing agents to be used. He will be governed in his selection not only by the existence of organic derangements such as cardiac or pulmonary disease, but also by the degree of mental fortitude with which the patient may be expected to respond to the anesthesia. It is deplorable that the value of the anesthetist as a bedside consultant is usually overlooked. For the geriatric surgical patient, such active participation becomes mandatory.

One needs hardly to be reminded that the first step in management must involve a thorough initial examination. A painstaking history, an exacting physical survey, appropriate laboratory studies, and such additional special procedures as may be indicated are prerequisites. Besides determining the course of the surgical illness with which the patient presents himself, the physician should seek to elicit information concerning concomitant diseases such as diabetes or hypertension, hypersensitivities, loss of weight, and the patient's reaction to previous accidents or operations. One may discern by physical examination such critical features as pronounced emaciation or obesity (either of which is an adverse factor from the operative standpoint (73)) emphysema, anemia, dehydration, distention, or cardiac arrhythmias.

The cardinal purpose of the preoperative survey should be a precise inventory

of the patient's reserves. This signifies a thorough evaluation of cardiovascular, respiratory and renal functions, not only at rest but, if possible, under simulated exertion. Senescence being heralded ordinarily by a state of catabolic ascendancy throughout the body, none of these three major systems will usually be spared. The physician's interest lies in appraising the existent degree of involvement and the possible further damage that may be withstood before leading to conditions inconsistent with survival. Many an old patient is a paradigm of Oliver Wendell Holmes' "One Hoss Shay," whose organism may endure long-standing burdens without danger, providing they are mild, but for whom a particular unfavorable condition may be the signal for complete collapse.

The problems which diabetes (74–79) and cardiovascular disease (43, 75, 80–89) present in the surgical geriatric patient are manifold, and necessitate the active cooperation of the internist. The reader is referred to the many papers on these subjects for detailed information. Notable is Master and Joffe's statement (90) that patients with severe heart disease tolerate even major operations if stringent precautions are taken to avoid anoxemia and further coronary insufficiency. A good result may be secured even in the presence of acute coronary occlusion or congestive heart failure when operation is obligatory. In less crucial instances, however, surgery should generally not be attempted within ninety days of the occurrence of coronary thrombosis, since it is estimated that about that length of time is required for the infarct to heal completely (91). Ostensibly, the heart would be expected to tolerate surgery better after healing had been accomplished. Rutledge (91) states that hypertension, even if severe, increases only slightly the risk of major surgical procedures, but this assertion remains unsubstantiated.

The customary laboratory studies should be made upon admission to the hospital, as well as those designated to evaluate surgical risk (92). In addition, concentration and dilution tests for the study of renal function are recommended (93). Spirometry (73) and oximetry (67, 94–97) are being used with increasing frequency, both for thoracic surgical problems (98, 99) and other operations, to obtain a measure of respiratory reserve.

The Four Horsemen of the Apocalypse in geriatric surgery are malnutrition, hypovolemia, hypoxia, and impaired vascular resiliency. A decline in the dietary status is a universal feature of old age (100, 101). This is contributed to by defective alimentation due to poor appetite or food faddism, gastro-intestinal dysfunction, and insufficiency of the glandular apparatus. Patients exhibiting long-standing malnourishment are said to be in a state of "chronic shock," the earmark of which is a chronically diminished blood volume (102, 103). Although complete restoration of dietary deficits can rarely be effected, and it is necessary to compromise in attempting to rectify general malnutrition, the specific influence on the blood volume is amenable to some degree of amelioration (100). This is accomplished primarily by replenishment with whole blood transfusions. There is ample evidence that replacement of deficits in plasma protein and red cell mass results in a much lower incidence of surgical complications, and enables the surgeon to carry out much more extensive procedures with far less risk (103–

110). Total blood volume is usually determined by means of the Evans Blue dye technique. In the presence of jaundice this method is unsatisfactory, and the human serum $I^{131}$-albumin technic should be employed (73). Beling and his associates (104, 106) plead that blood volume studies be made on all elderly surgical patients, and that all deficits be corrected quantitatively. When it is not possible to carry out a blood volume determination, a rough calculation of blood requirement may be made on the basis of nutritional deficiency alone. It is estimated that there is a 50-cc. deficit in blood volume for every pound of recent weight loss, and this figure had proved to be useful in actual practice (111). Another simple guide is to allow 500 cc. of whole blood for every 7-point deficit in the hemoglobin level under 70 per cent (112) or for every 3-point deficit in the hematocrit reading under 50 (113). In their report on plasma substitutes, Seeley and Pulaski (114) emphasized that these agents should be thought of only as adjuncts for "volume expansion," and that fresh whole blood, due to its oxygen-carrying capacity and space-occupying function, is still the choice as a supportive agent. Because plasma substitutes pass freely through the capillary membrane, and water follows them when they leave the intravascular space, their use in the debilitated, hypovolemic patient is fraught with danger in the long run.

Caloric sustenance is furthered by the use of food supplements and alcohol in the dietary regimen. However, the chief component lacking in a state of nutritional deprivation is protein (115, 116); paucity of protein is almost tantamount to failure in the outcome of an operation. Hypoproteinemia increases the peril of shock and infections, contributes to retardation of healing and prolonged convalescence, and creates unsatisfactory situations in abdominal surgery because of edema of the bowel. The role of protein in surgical patients has been reviewed thoroughly by Wilensky (117), Elman (118), Chassin (119), and Cole (120). Blood transfusions and parenteral administration of amino acids constitute a prompt method for bolstering a waning nitrogen balance. Protein losses are cumulative, and cannot be replaced by any other food element. The rapid replacement of protein is difficult, and need not be complete (113). The laboratory determination of the total protein concentration in the blood is at best an unreliable index of protein body stores, especially when there is coexistent dehydration. Hypoproteinemia should be suspected before the plasma protein concentration falls below normal or edema appears. Anorexia, continued weight loss, and retarded gastro-intestinal motility may be the signs of impending hypoproteinemic complications. It is interesting that hemoglobin will be preferentially synthesized first under any program of protein replacement before tissue or plasma protein deficits are restored. This serves to underscore the need for correction of anemia by blood transfusion first in the process of correcting an over-all protein deficiency (121).

Hypovitaminosis is also a significant factor. Deficiency of vitamin C delays the healing of tissues. The various members of the vitamin B complex are concerned with carbohydrate metabolism, and aid in the utilization of protein. Vitamin K is involved in the mechanism of blood coagulation. These vitamins should be given routinely in sufficient dosage by either the parenteral or oral

route. Thiamine cannot be added to amino-acid solutions because of chemical incompatibility (113). It is well to remember that institution of a wholesome diet in a patient suffering from inanition may be characterized by some loss of weight during the first few days. This is ordinarily a favorable sign, since it usually signifies reduction in the edema fluid which is often diffusely distributed throughout the body, though not demonstrable grossly (120).

Rupert (122) has discussed the significance and influence on prognosis in elderly surgical patients of disturbances in the acid-base balance of the blood. The regulation of fluid and electrolyte balance in the aged has been reviewed recently by Bland (123). The necessity for restraint in giving salt and fluids has been noted by Ziffren, Zager and Cullen (124). The problem is complicated by incompetent functioning of the cardiovascular adjusting mechanisms, and the consequent danger of inadvertently precipitating pulmonary edema and congestive heart failure. It is important to regulate the fluid volumes very carefully, and to administer them slowly so as not to tax an already enfeebled system. Patients in this age group seldom require more than 2 liters of fluid daily (124) in the absence of unusual losses. In general, the rate of flow should not exceed 1 liter per hour. Elman (108) stated that, in special cases, a manometer should be inserted in the infusion set in order to register venous pressure; as long as the pressure is maintained under 100 millimeters of water there is little, if any, danger of overloading the circulation. However, in actual practice, there can be no predetermined rule for the rate of infusion. Constant observation for clinical evidences of augmented venous pressure (as seen in the neck and arms) and of the state of the pulmonary circulation (as determined by observation of respiration and auscultation of the bases of the lungs) will serve as a gauge for regulating the rate of flow. Absence of thirst, a urinary output exceeding 1 liter daily, and a low urinary specific gravity are evidence of adequate hydration. Control of fluid and electrolyte balance can be more readily achieved on the basis of computing daily intake and losses than on the vagaries of blood chemical determinations, which may be either deceptive or unrevealing. Scribner, Power and Rynearson (125) found that by conducting such studies on water and chloride alone, maintenance of equilibrium became a relatively simple matter. They recommend this method as especially helpful when extensive laboratory service is not readily available. The intravenous route is the safest means of administration of parenteral fluid. Hypodermoclysis is inadvisable, especially in patients suffering from dehydration, salt deficiency, or shock, since subcutaneous infusion of hypertonic non-electrolyte solutions may result in dangerous translocations of body fluids and in peripheral vascular collapse (126, 127). The use of hyaluronidase in such circumstances is hazardous, since it may very well intensify this reaction (128).

Preoperative medication has to be given with great care in the aged because of impaired metabolism (129, 130), idiosyncrasies, unpredictability of response, or dangerous side-effects (131, 132). Narcotics and sedatives are particularly notorious for actually producing disorientation and excitability in some aged patients (97, 131). Rovenstine (133) urged that morphine be excluded from the preoperative regimen in all patients over 70 years of age. Barbiturates are

dangerous because of their depressive action on the vital functions. It is generally advisable to prescribe a fraction of the regular dose, and to supplement this cautiously when necessary (19, 134). Bernstine and Golden (135) believe that Demerol (50 mg.) plus atropine sulfate (0.4 mg.) supplies the ideal preoperative medication, sedation being obtained with minimal depression. Rovenstine and Betterman (136) enumerated the many advantages of Demerol as a substitute for the opiates, pointing out that it is a bronchodilator, that it decreases secretions, that it does not depress respiration to the same extent as comparable amounts of morphine, and that it produces no appreciable alteration of the blood pressure in the recumbent patient. With modern anesthetic supplements, the need for heavy preanesthetic medication to facilitate induction and sustain anesthesia is past.

One may expect to find with increasing age a greater incidence of hypersensitivity to antibiotics (137). These drugs should be given only after the history discloses the absence of previous allergic manifestations (71). Foster and Copeland have discussed the problems involved in the use of antibiotics in surgery of the aged (137).

Although it is agreed that cardiac glycosides should be given promptly in cases in which incipient heart failure or arrhythmias present themselves (43, 91, 138), their routine use preoperatively as recommended by Christian (139) awaits further trial. Raisbeck (140) has discussed the indications and dosage considerations in the use of digitalis preparations in the aged. The management of edema in the elderly has been reviewed by Miller (141).

The preoperative administration of sex steroids in geriatric patients has been suggested (142, 143) because, through their anabolic action, these agents increase muscular power, induce a gain in weight and enhance the feeling of well-being. Such use of gonadal hormones has had limited application to date.

Cortisone and ACTH have also been advocated for the supportive treatment of patients who have poor adrenocortical function, and who may not have the wherewithal to tolerate the stress of operation (144–149). Fromer (150) and Adams and Souders (151) reported that in some cases of asthma or emphysema, a course of corticotropin will provide maximal improvement in pulmonary function. The use of these steroids should be tempered, however, by the knowledge that when given over a long period of time they may induce excess retention of fluid and adrenal insufficiency (152). Although the corticoids do improve the appetite, much of the observed sharp gain in weight is undoubtedly attributable to water (149).

A preoperative therapeutic factor, the importance of which cannot be emphasized enough, is the proper psychologic buttressing of the patient. Hushed discussions at the foot of the bed only augment the patient's apprehension. The author is reminded of a poem by Arthur W. Bell (153) in which the following stanza appears:

> "Myself grown old do fearfully frequent
> Grim hospitals and hear great argument
> About me, but with luck have heretofore
> Come out by the same door wherein I went!"

It is incumbent on the physician to inspire the patient with hope of recovery. Elderly persons are usually greatly alarmed, but attempt to hide their fears under a veneer of stoicism or fatalism. The psychic responsiveness to stress, as measured by Pincus (154) and Flynn (155), appears to be the same in the aged as in the young, provided preparation has been adequate. Both surgeon and anesthetist should approach the patient with candor, cheerfulness, sympathetic understanding, and encouragement. The crucial influence on subsequent anesthesia of masterfully directed reassurance and the dispelling of undue anxiety is well borne out in the experience of most surgeons. Despite this evidence, the physician is too often derelict in this preoperative psychic fortification. Instead, sedatives are prescribed—to the detriment of the patient.

## OPERATIVE CONSIDERATIONS

A major hazard in geriatric surgery is the marked tendency toward occurrence of shock. This derives from: (a) a less intense adrenocortical reaction to injury (156), (b) an inordinate sensitivity to anoxia (157, 158) and abrupt fluctuations in blood pressure, and (c) a sluggish compensatory response to hemorrhage. These deleterious effects may be counteracted in part by optimal emotional preparation, in order to obtain satisfactory relaxation and a tranquil patient. Positioning on the operating table is important, in that significant shifts in blood volume may occur as a result of maintaining the patient in extreme postures (such as the lateral or the lithotomy positions) for prolonged periods of time (68). Sudden positional changes of the anesthetized patient may initiate hypotension, and thus set the trigger for circulatory insufficiency, thrombosis, embolism, and infarction (159).

Lorhan (112) pointed out the need to protect the patient's joints and bony prominences with padding in order to obviate pressure necrosis (160), which is very difficult to treat in elderly persons (161). Along these same lines, the surgeon and his assistants must abstain from rigorous traction or use of the patient's body as a leaning-post during the operation. Ill-distributed pressure on the limbs throughout the course of an operation may cause serious harm to nerves and vessels, and attrition of the skin. Tourniquets should not be employed for long intervals on the patient's extremities. Also, the use of leg veins for infusions should be avoided, if at all possible, in an effort to prevent the development of thrombophlebitis (17).

Cutler, Makel and Beecher (162) found that of 300 patients under general anesthesia, 26.3 per cent regurgitated gastric contents, which were in turn aspirated in 49 per cent. In 70 per cent of the cases of aspirated gastric contents, an intratracheal tube had been inserted. Accordingly, Dodd (138) and Anglem and Bradford (163) advised a tube with an inflatable cuff despite certain disadvantages associated with its use. Aspiration of gastric contents may evoke pulmonary abscesses and a necrosing, septic bronchitis from which debilitated patients seldom recover. Intubation is easily accomplished because so many of these patients are edentulous and have a large glottis.

The anesthetic procedure and the agents selected should be adapted to the

individual case (164). They will depend on the patient's social and systemic history, on the scope of the operation planned, as well as on any of the patient's physical defects. In aged persons, not only have the lungs lost some of their elasticity, but often the chest expansion is limited by kyphoscoliosis and rigid costal cartilages. Ziffren and Cullen (165) have summarized this basic approach of individualizing anesthesia as follows: "There is no justification for employing a specific drug or method in all aged persons, simply because they are old; there are many other factors influencing the choice of anesthetic. For example, in one elderly patient requiring hernioplasty, infiltration or regional analgesia may be better because the patient is cooperative, he is thin, and the hernia is easily reduced. In another patient spinal analgesia may be better because he is obese, the hernia is easily reduced, and he prefers to remain awake during the procedure. In still another patient, inhalation anesthesia with cyclopropane may be better because he is uncooperative, has severe hypertension, has a hernia difficult to repair, and early awakening is preferred." Regardless of the anesthetic employed, a constant unstinted supply of oxygen is essential, a clear airway must be maintained, and resuscitation apparatus must be at hand. The success of anesthesia is a function of the experience and perspicacity of the anesthetist, aside from the judicious choice of anesthetic combinations (167, 168).

Much of the literature on geriatric surgery delves into the advantages and disadvantages of various anesthetics (135, 169–184). Although a review of this aspect of the subject is beyond the scope of this paper, a few concomitant features may be noted. Procaine compounds given preoperatively are said to preclude the development of cardiac arrhythmias that may occur under cyclopropane anesthesia (185). Barbiturates in small doses may be given prophylactically as a precaution against procaine reactions (186). Muscle relaxants (187), and succinylcholine chloride (69) in particular, are being viewed with increasing favor as complementary anesthetic medication. The duration and depth of anesthesia directly affect morbidity and mortality in the geriatric patient. Lorhan (112) claims that the mortality is approximately one fourth as great if the operation is longer than one hour in duration, and that this figure increases progressively as the time increases. Occhipinti (188) elaborated recently on the essentials of anesthesia for cardiacs undergoing general surgery.

The fundamentals of operative technique are in no way different from those in younger individuals, except that the limits of safety are narrowed. There should be no latitude in hemostasis or coaptation of tissues. Speed and gentleness are the prime requisites in surgery of the aged (189), the morbidity and mortality being adversely influenced by increased duration of the operation. Patients of advanced years are especially intolerant of trauma. Strong-arm surgery is interdicted most in the geriatric patient. When possible, it is advisable as a matter of routine to obtain material from the affected organs for smear and culture (137). This permits examination for selective bacterial sensitivity with a view to applying specific chemotherapeutic measures. Elderly persons succumb to infections readily, so that all feasible antibacterial precautions should be exercised (109).

## POSTOPERATIVE CONSIDERATIONS

An aim in rapid and uneventful postanesthetic recovery is that the patient be awake at the termination of the surgical procedure (112). If this cannot be accomplished, strict precautions must be applied in transferring the patient to the Recovery Room. The operative position should not be changed. Occasionally, it may be even advisable to transport the patient while still on the operating table.

It is particularly important to make frequent determinations of the blood pressure and pulse rate postoperatively in elderly subjects, since deviations from the normal level are ill tolerated. Norepinephrine is an effective, but dangerous, crutch in the control of blood pressure (67).

The patient should be turned from side to side frequently. When he regains consciousness, he must be encouraged to cough and take deep breaths at repeated intervals in order to offset atelectasis and bronchopneumonia, these being contingencies to which older individuals are particularly prone (190). In the supine position, the accumulation of viscid bronchial secretions in the basal pulmonary segments is aggravated because of reflex fixation of the abdominal muscles and high splinting of the diaphragm. Retained secretions must be removed by frequent suction and cleansing of the pharynx and tracheobronchial tree (191). Very tenacious mucus may have to be withdrawn by bronchoscopy. The necessity for repeated tracheal aspiration may be overcome by the inhalation of a mist of mucolytic drugs introduced by an appropriate nebulizing apparatus (151). The danger of surface-active agents is that, if not regulated carefully, they may induce such extensive liquefaction that the patient "drowns in his own secretions." Some authorities advise elective tracheotomy postoperatively in every geriatric person (192–196). The usefulness of routine application of this modality in the reduction of respiratory-tract complications awaits confirmation. In the elderly edentulous individual, the effect of tracheotomy in reducing dead space is immediately appreciated. Ordinarily, when the patient's dentures are removed the lips and cheeks sink in on inspiration, forming an obstruction which interferes with respiration and tires the patient (138). The aged person suffering from emphysema, bronchiectasis, or asthma is greatly helped postoperatively by mixtures of helium with oxygen (112).

Sedation in the postoperative period is conditioned by the principles that apply in the preoperative period. In addition, postoperative sedation endangers the patient by dulling the cough reflex (131) and accentuating bronchospasm and sluggish respiratory efforts. After operation, there is also an even greater inability to metabolize fixed drugs such as morphine. Abdominal and thoracic pain may be relieved by intercostal block with procaine (184, 197). Postsurgical pain may be eliminated by infiltration around the wound with efocaine (198), or by intravenously administered alcohol or procaine (191).

If the patient is to be placed in an oxygen tent, he should be informed of that possibility prior to operation, since the tent signifies death in the mind of the laity, and an impressionable or hyperexcitable patient may experience veritable terror when regaining consciousness in such an unexpected environment. The oxygen tent is at best an air-conditioner of low efficiency in hot and humid hospital

wards. The psychic trauma may be circumvented by administering the oxygen through an intranasal catheter. Besides being valuable from the viewpoint of respiratory physiology, oxygen aids materially in decompression of the intestines, in that it replaces the nitrogen accumulating in the distended gut. All catheters, whether for oxygenation or suctioning of gastro-intestinal contents should be withdrawn at the earliest opportunity. The presence of a catheter inhibits coughing and increases the amount of mucus secretion, which may lead to atelectasis and subsequent pneumonia. Not infrequently the catheter causes ulceration of the pharynx and esophagus, which interferes with speedy resumption of eating (199). When prolonged use is necessary, plastic tubes are much less irritating than rubber ones and are better tolerated by the patient (162).

An indwelling urinary catheter may be left in place for approximately one week after operation (200), but should then be removed in order to lessen the possibility of cystitis (17). O'Conor and Rhoads (201) have discussed the management of complicating urinary-tract infections in elderly patients. Intake and output of fluids should be charted accurately. Postoperative anuria may be the first indication that the patient has incurred a transfusion reaction during the operation (71).

Vascular accidents constitute one of the most serious postoperative sequelae. Rupture of diseased brain vessels in persons of advanced age is not uncommon following even a moderate increase in blood pressure. The aged are extraordinarily susceptible to thrombosis (especially in the leg veins) due to venous stasis and the reduction in blood flow which accompanies damage to the arteries from decreased resiliency, narrowing, and intimal thickening. Frequently there is a close temporal relationship between acute circulatory illness and physical or psychologic stresses (155).

Much has been written about the hazards of prolonged immobilization, particularly in regard to the inception of thrombophlebitis and pulmonary embolism, and of joint, bone and muscle atrophy. The first named complications stem from vascular stasis, and the latter from the increased tendency toward disturbances of the locomotor system. It has been definitely established that there is crucial need for early termination of bed rest, and for ambulation. Exceptions to this rule are the presence of unusual cardiovascular strain, bacterial peritonitis, recent coronary occlusion or thrombosis, and pulmonary embolism. Even in these cases, it is important to change the patient's position frequently in order to avoid decubitus ulceration and further lagging of the circulation. Although the wisdom of early ambulation is generally unquestioned in patients in whom the foregoing deterrents are inoperative, the value of this regimen is often marred by ineptitude in performance. It is therefore imperative that the physician devote some time in explaining to the patient and attendants what is expected of them. Termination of bed rest should never be sudden, and must be preceded by early and continual exercise of the lower extremities, both in the form of isometric contraction of muscles and in passive motion. Mobility does not mean sitting on a chair with a sharply angulated seat that may press on the calves and obstruct venous return in the pelvis (17); nor does ambulation signify carrying of the patient from bed to chair. Actual walking, with small strides and

under vocal and physical assistance, is what is desired. Only thus may a brisk blood flow in the peripheral veins and vena cava be fostered.

If good technical principles have been observed in the operation, there should be no impairment of wound healing in the aged (108), unless it be in the extremities because of arteriosclerosis interfering with vascularity of the part. Interference with wound-healing is more likely to result from straining at the bed-pan—the various evil sequelae of which have been expounded by many writers. Champions of the commode are gaining new adherents every day.

The best treatment for phlebothrombosis and thrombophlebitis is still prophylaxis (202). Some physicians apply elastic bandages to the patient's lower extremities at the conclusion of all operations (17, 71, 163, 196, 200, 203, 204). Williams *et al.* (205) caution against the use of elastic stockings in patients whose arterial circulation in the legs is compromised. Elevation, exercise and massage of the legs should be carried out, as well as repeated checks for tenderness of the calves and for Homans' sign. Evans (206) warns that in the aged and debilitated patient pulmonary embolism is often manifested merely by episodes of suffocation, fever, and an increase in the pulse rate. Pleuritic pain and hemoptysis are absent; the roentgenograms either show nothing abnormal, or just small patches of atelectasis. Evans prescribes anticoagulants in such cases. Prophylactic heparinization and/or vein ligation have some proponents (207), but these methods have not met with widespread adoption (200).

The tendency, unfortunately, is to overtreat with fluids and electrolytes. It is far better to err on the side of moderation, giving little rather than too much, and thus avoiding inundation of the patient's lungs or straining already burdened kidneys. One should adhere to the good rule: that which is lost should be replaced—no more, no less (208). Infusions of sodium chloride are unnecessary during the first two to four postoperative days, because of the adrenocortical influence on salt retention and because such infusions may also exaggerate a potassium deficiency (209, 210). Moreover, in less severe protein depletion not accompanied by visible edema, infusions of sodium chloride may precipitate frank edema (211). Although the postoperative excretion of potassium is usually lower in older than in younger patients (212), considerable amounts may be lost through protracted vomiting, diarrhea, or evacuation of great volumes of secretions from the alimentary tract (213, 214). Accordingly, one should be on the alert for signs of hypokaliemic alkalosis, which is relatively more frequent in older patients because of the preceding mild hypopotassemia attendant on chronic malnutrition. The clinical and diagnostic features of this syndrome and its management are described in several texts. Hypopotassemia may be held in abeyance by restricting intravenous fluid therapy and limiting the duration of gastric and intestinal tubal drainage. An appetizing oral diet should be started as soon as the patient's condition permits it; the superiority of the oral route of feeding remaining unexcelled (2). Because impaired dentition is relatively commonplace in the aged, the physician should plan a well balanced diet of soft or liquid food. This is usually best accomplished through multiple small meals containing sufficient fat to maintain the appetite (215).

The importance of good nursing care in the aged cannot be overemphasized

(216). Its essentials have been discussed by Beland (217). Older patients not uncommonly become confused, and should be protected by sides on the bed, especially at night (204). Sedgwick and Bartels (218) have reviewed the treatment of chronic leg ulcers in the aged. The possibility of parotitis is a bugbear often invoked in order to institute good mouth hygiene; actually, parotitis is relatively rare, but this should not obviate scrupulous oral or general antisepsis. In all cases, it should be urged that there be persistent nursing supervision only when indicated—a goal of rehabilitation being that the patient should fare for himself eventually, and not become dependent for ordinary minor requirements on the presence of hospital personnel. It is a common observation that no patient is more quickly nursed to death than the geriatric patient (66). Self-sufficiency must be motivated by interest and support of morale. If apathy be permitted, it will initiate a vicious cycle of anorexia, asthenia, inanition and dehydration that may become irreversible and lead to otherwise preventable death. The conduct of postoperative care in elderly patients is the physician's responsibility and should not be delegated to someone unfamilar with the early signs of complications. When these signs appear, the disorders must be combatted vigorously because of the impaired recuperative powers of the aged in the face of additional insults to their precariously maintained homeostatic mechanisms.

## SUMMARY

The increasing number of geriatric patients with surgical disorders is due to the lengthened lifespan accruing from improved health measures.

Major surgery in the elderly patient is not contraindicated, either on the basis of age or the presence of concurrent diseases, when such operative intervention may mitigate severe pain or increase longevity. Despite the presence of serious invalidism and metabolic derangements, much can be accomplished in improving the patient's status through energetic corrective measures subsequent to a conscientious appraisal of existing deficits and reserves. The regulation of concomitant nonsurgical disorders, and individualization of operative and anesthetic procedures can be achieved only through the concerted efforts of the surgeon, internist and anesthetist at the bedside. Tests of function should have as their objective the determination of margins of safety under stress, rather than under resting conditions.

In the aging patient, chronic malnutrition, hypovolemia, hypoxia and defective vascular resiliency are the major factors which complicate the problems of management. Deficit of protein is the single most important feature requiring correction in order to diminish surgical risk. The extent of impaired blood volume should be estimated, and quantitative repletion effected by means of whole blood transfusions. Attempts at improving protein stores without first correcting anemia are generally ineffectual. Medication requires meticulous adjustments in dosage in order to circumvent individual idiosyncrasies and reactions to drugs. Fluid and electrolyte therapy is hazardous if poorly controlled, because of the danger of flooding the patient's lungs and inducing cardiovascular disturbances. Attention to deranged bodily function without due consideration to psychic

fortification as part of the overall preoperative preparation is inconsistent with proper management.

The technical features of operation are similar to those in younger patients but the details require more attention inasmuch as the elderly person is intolerant of even minor degrees of trauma, hypoxia, or change in blood pressure. Speed and delicate handling of tissues are the keynotes to good technique. During the entire procedure, the patient's body should be well protected from unwarranted pressure or traction. The anesthetic should be chosen on an individual basis, and its selection depends upon the nature of the underlying surgical disorder, on the physical abnormalities and medical history of the patient, and on the anesthesiologist's experience and preferences. Regardless of the anesthetic employed, the oxygen supply must be adequate throughout operation, and the airway at no time obstructed.

The principal aspects of postoperative management involve suitable precautions to forestall the development of complications to which the elderly subject is especially prone. These complications include respiratory disturbances, infections, vascular accidents, musculo-skeletal damage, and electrolyte imbalance. Early mobilization and ambulation should be instituted in all cases, since prolonged bed-rest has many deleterious effects. The removal of all catheters, and prompt resumption of oral feeding when possible, are important considerations in postoperative rehabilitation. Although assiduous nursing care is a vital component of management, it should be carried out with restraint in order to permit the rapid return of self-sufficiency on the part of the patient.

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# MAJOR SURGERY IN PATIENTS OVER 80

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When one discusses geriatric surgery it does not usually concern octogenarians. During the past year 6 of our elderly patients were subjected to major extensive surgery. The youngest in the group was 81 and the oldest 88 years of age. The oldest was operated upon for a massive colloid goiter which was causing asphyxia secondary to tracheal compression. The remaining 5 patients were subjected to abdominal surgery (Table 1). In these 5, two major problems presented themselves prior to surgery. They concerned the presence of azotemia and the choice of anesthesia.

## AZOTEMIA

It is possible that the patient over 80 may have all three etiologic types of azotemia: 1) prerenal, 2) renal, and 3) postrenal. Of the three, the most commonly observed acute type is prerenal. Azotemia (elevation of the non-protein nitrogenous constituents of the blood) of rapid onset associated with acute abdominal symptoms is usually prerenal in origin. It is the result of loss of chlorides secondary to vomiting, diminution in fluid intake, diarrhea, or inability of a diseased colon to absorb fluids. In elderly patients these symptoms do not have to be of long or frequent duration to produce azotemia. One or two episodes of vomiting without intake of food or water for twenty-four hours is often sufficient to institute a rise in the levels of blood urea and urea nitrogen. This is because, in persons of advancing years, there may be dormant subclinical states of renal azotemia of varying degrees as a natural consequence of renal arteriosclerosis and/or arteriolarsclerosis with or without another vascular disease of the kidney. Hence a combination of prerenal and renal disturbances will promptly precipitate azotemia. In our series, postrenal azotemia was associated with the prerenal type in 1 of the six patients. The subject in question was an 81-year-old man with adenocarcinoma of the ascending colon and benign prostatic hypertrophy; the latter was the cause of the postrenal azotemia, as it acted as a mechanical block to the outflow of urine. Prostatic hypertrophy is one of the commonest causes of postrenal azotemia in men, and uterine fibroids with compression of one or both ureters is the most common offender in women. Although azotemia is a serious situation in the elderly, it can be corrected easily by the judicious administration of intravenous fluids. Saline solutions should be given with caution, because an excess of sodium ion can easily disturb the fluid balance and precipitate pulmonary edema. With the correction of the azotemia, thought can then be given to the choice of anesthetic prior to surgery.

## ANESTHESIA

Within the experience of each surgeon there comes a time when one type of anesthesia gives way to another. In previous years spinal anesthesia was pre-

TABLE 1

*Data on 6 Geriatric Patients Undergoing Major Operations*

| Patient | Age | Diagnosis | Operation | End-Result |
|---|---|---|---|---|
| Mrs. A | 88 | Adenomatous colloid goiter | Thyroidectomy plus tracheotomy | No postop. complications. Discharged from hospital |
| Mr. P | 83 | 1. Cancer right colon<br>2. Prostatic hypertrophy | 1. Resection of colon plus ileocolostomy (primary anastomosis)<br>2. Prostatectomy | No postop. complications. Discharged from hospital |
| Mr. K | 81½ | Intestinal obstruction due to Meckel's diverticulitis | Resection of diverticulum; lysis of adhesions | No postop. complications. Discharged from hospital |
| Mrs. H | 82 | Cancer of descending colon | Rankin resection of colon; colostomy | No postop. complications. Discharged from hospital |
| Mrs. H | 83 | Common-duct stone; cholecystitis with calculi | Cholecystectomy and choledochostomy | No postop. complications. Excellent recovery at home |
| Mr. L | 86 | Cancer of common bile duct | First-stage resection, Roux Y operation | No postop. complications. Discharged to home after jaundice subsided |

ferred for abdominal procedures in geriatrics because the patient was not asleep and forceful active respiration was in evidence or could be stimulated by encouraging the patient to breathe deeply. However, when it was found that pulmonary complications occurred equally following spinal and following general anesthesia, it became apparent that the spinal method was not the preferable anesthetic procedure. Elderly patients prefer to be asleep during surgery. All in all, the spinal method has lost its allure.

Preference is given to a balanced form of anesthesia combining two or more anesthetic agents. Dilute pentothal (0.5 per cent) is preferred for induction. In our series of abdominal operations in geriatric patients, anesthesia was maintained with cyclopropane and 75 of 80 per cent oxygen, supplemented with muscle relaxants (such as anectine or curare) when needed. Pressor drugs (Methedrine, Levophed) were employed as indicated.

Although balanced general anesthesia is the preferred method, there is no objection to the use of the spinal method. When spinal anesthesia is used in geriatric surgery, satisfactory results may be obtained with small doses of novocaine (75 to 100 mg.) supplemented with 0.5 per cent solution of sodium pentothal (drip method) and oxygen, plus the administration of pressor drugs to maintain vascular tonicity.

In elderly patients who are known to be poor risks, we have used local in-

filtrating novocaine anesthesia in other cases than those in the present discussion. Complete anesthesia, however, did not depend upon the local novocaine exclusively. Supplementary agents were employed. The supplements invariably were 0.5 per cent sodium pentothal with muscle relaxants. In certain instances cyclopropane was used with an equal mixture of 100 per cent oxygen. Cyclopropane has not, and is not, used if cardiac arrhythmia is present. Past experience has taught that in the presence of cardiac arrhythmia, the administration of cyclopropane may precipitate a partial heart block. In poor-risk patients and in those upon whom extensive operation is contemplated, infusions of fluid and blood and the judicious administration of drugs to maintain vascular tone are the indispensable adjuncts of geriatric surgery.

## COMMENT

In the 6 patients listed in Table 1, electrocardiograms were taken. No acute lesions were revealed, but all the records showed either left axis deviation, myocardial damage or coronary artery disease. In roentgenograms of the chest no pulmonary abnormalities were seen, but there was deviation from the normal cardiac condition in all cases. These deviations were interpreted as enlarged cardiac shadow, increased size in the aortic bulb and/or evidence of arteriosclerotic changes in the aorta.

Two patients in the group are worthy of special mention because further surgical procedures would have been contemplated under different circumstances. The fourth patient in Table 1, Mrs. H., had a colostomy which could be closed eventually if she so desired. However, she became accustomed to the colostomy, and it is doubtful if any further operation will be performed. The sixth patient, Mr. L., had the first-stage procedure usually carried out to by-pass the block which is producing jaundice. When this is performed, it is tacitly implied that the surgeon will undertake the second extirpative operation about six weeks later. More than six weeks passed since the first operation and the patient refused additional surgery. He is 86 years of age. If he remains comfortable for the next four years, the first-stage operation will have been well worth while.

## SUMMARY

1. A report of the surgical results in 6 patients over 80 years of age is presented.

2. All underwent major operations without postoperative complications, and were discharged from the hospital.

3. Major preoperative problems associated with surgery in octogenarians are discussed.

4. Age is no contraindication to major surgery when adequate preoperative care is taken, and the anesthetic is judiciously administered.

# HOST-TUMOR ANTAGONISM. VIII. THE PSYCHOLOGIC COMPONENT INVOLVED IN THE HOST RESISTANCE TO CANCER*

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## INTRODUCTION

Whether or not a psychosomatic influence is involved in the development or spread of cancer is not certain at the present time. So little is actually known of the factors that control the growth of cancers, that a psychologic factor is a possibility, albeit a minor one. This essay lists some of the evidence for this approach. There is one disease (carcinoma of the pancreas) that may mimic a psychiatric illness in its early evolution. This does not necessarily mean that it is a psychiatric illness in its incipiency, but rather that the early symptoms are so minor that they are taken to be of a functional nature. However, it is also possible that this cancer may secrete a chemical substance that induces psychiatric symptoms. There is one tumor, metastasizing carcinoid, that actually secretes a substance, serotonin, that has been shown to have a profound role in cerebral function.

## I. EVIDENCE FOR A PSYCHOSOMATIC APPROACH TO THE PROBLEM OF CANCER

Our inability to determine the exact factors that differentiate a patient with a slow-growing tumor from one with a fast-growing tumor has lead to the possibility of a psychosomatic influence. Even so eminent a surgeon as Max Cutler (1) feels that the curious variations in the natural history of cancer may be on this basis. He suggested that in certain patients with rapidly growing tumors, the cancer was being utilized psychologically as a passive form of suicide. He stated that although patients were given the same surgical and radiologic attention, the eventual outcome varied considerably, depending on the attitude of the individual concerned. He quoted the striking case of a patient with widespread breast cancer, which had metastasized to the supraclavicular and cervical lymph nodes following radical mastectomy, who had remained in good health for nine years. This patient stated that she was sure that she would be perfectly well. She could not understand the doctor's concern about her.

Cutler mentioned another patient, a woman of 78, who had lived for ten years with untreated cancer of the breast because she refused surgery and radiation. She was a religious fanatic, and she had a paranoid reaction shortly after the onset of the disease. She "didn't need treatment because God was saving her." She is said to have been vituperative in the expression of her rages.

P. M. West (2), an enzyme chemist, who has contributed much to the biochemical literature on cancer, also believes that the affective state of the patient may

* Parts I–VII of this study have been published in the July, August, November (1956), April, May, June and August (1957) issues of this Journal.

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determine the speed of growth of a cancer in the individual case. He and a colleague (F. W. Ellis), working together, became amazed at their ability to predict the eventual fate of a particular patient with cancer. At first, all they could say about the distinguishing characteristics, was that those that got along well with cancer were "dull," and those who did poorly were "bright" individuals. Others at medical meetings in their institution also noted a disparity in 2 early cases of rectal carcinoma—one, a "worthless rascal," was apparently cured; the other, "a prince of a fellow," was dead of generalized metastases in a few months.

Inevitably, various psychologic tests were tried on both the "fast" and "slow" patients. (These designations refer to the growth of the cancer). Blumberg (3), working with West, noted that the psychologic characteristics of the patients with fast-growing cancers were greater defensiveness, more anxiety, and less ability to release tensions through motor discharge, either verbal or physical, when compared to the patients with slow-growing cancers. Defensiveness, as here defined, is the state in which the patient is motivated to appear "good" and refers to his motivation in order to give the impression that he is less disturbed than he really is. Patients who seemed to possess exceptional resistance to the growth of neoplasms appeared to be successful in avoiding or reducing emotional stress by one or more of the following means: normal outward activity, psychopathic activity, or successful anxiety-reducing activity such as conversion hysteria or psychotic activity. Blumberg's conclusion was that psychologic factors are not necessarily basic in determining the resistance of a cancer patient to the growth of an established cancer, but they may be of enough significance to constitute a new approach to the complex problem of host resistance.

Under the circumstances, the frequency of cancer in psychotic persons becomes of great importance. A recent article by Scheflin reviews the records of all psychotic patients and of patients with proved cases of cancer at the Worcester State Hospital between 1928 and 1942 (4).

There was a suggestive, but not statistically significant, increase of carcinoma of the pancreas in schizophrenic patients as compared to patients in the general population.

In the psychotic population, cancer is significantly more frequent than in the general population. The increase is due to the greater incidence in the group of cases termed senile psychosis and psychosis with cerebral arteriosclerosis. In these diagnostic groups, many patients are admitted who already have advanced cancer. When these groups are not included in the tally, there is no significant difference between the psychotic and general populations in regard to the frequency of cancer.

In the catatonic, hebephrenic and schizo-affective types of schizophrenia, the cancer rate was less than expected. In the paranoid group and in paranoid conditions, cancer death rates were abnormally high. These patients also died of cancer at an unexpectedly early age. Scheflin states that cancer is apparently relatively rare in psychosis characterized by depressive reactions.

These interesting findings have been previously noted by others. For example, Lewis (5) divided schizophrenic patients into two classes:

1. Regressive (catatonic and hebephrenic). In this group atrophy, hypoplasia and fibrosis are common but malignant changes are rare.

2. Hypercompensatory (paranoia and paranoid states). In this group hypertrophy, hyperplasia and malignant states are common.

White (6) tabulated the incidence of malignant neoplasms in schizophrenics and found 136 per thousand in the paranoid group but only 43 per thousand in the catatonic group. This was a significant difference, and the reason for it merits careful attention.

Whether there is actually a causal relationship between mental influences and the rate of cancer growth remains, to say the least, uncertain. Perhaps the best way that this can be illustrated is from a case reported by Dr. Joseph Weinberg (7), the surgical chief at the Long Beach Veterans Administration Hospital, California.

A woman had been operated on for cancer of the stomach. The operating surgeon considered the growth to be non-resectable, so he closed the wound and notified the patient that she had incurable cancer. Feeling that medicine had little to offer, she turned to Christian Science. Dr. Weinberg first saw her at that time; she was secure, untroubled and very placid. It was natural to think of this patient as an apparent cure of cancer through favorable psychosomatic influence.

Twenty years after the first operation, cancer of the breast developed in this patient, during a time when she was deeply under the influence of Christian Science teaching. This cancer progressed with great rapidity and the patient died within a year. Dr. Weinberg commented that the original diagnosis of non-resectable cancer of the stomach was likely erroneous. Had the error not been made, and had the patient been operated on for the breast malignancy, she would undoubtedly have had a better fate. He further stated that a great burden of proof and responsibility rests on those who pursue unproved hypotheses, in order that no harm be done to the unfortunate victims of this scourge.

## II. CARCINOMA OF THE PANCREAS PRESENTING AS PSYCHIATRIC ILLNESS

It is well known that the early symptoms of some patients with carcinoma of the pancreas may be entirely in the psychic sphere. This was first pointed out in 1923 by Lovell (8) who described a case of agitated melancholia with severe anxiety in which a clinical diagnosis of carcinoma of the pancreas was finally made. It has been estimated that more than 10 per cent of patients with carcinoma of the pancreas have a psychiatric problem. Yaskin (9) noted that the psychic symptoms sometimes found in these patients were anxiety, obstinate insomnia not due to pain or relieved by the usual barbiturates, depression with crying spells, and a conviction of imminent physical danger.

The present author (10) has described a case of carcinoma of the pancreas, treated during the early weeks of illness for psychosomatic symptoms:

> The patient was a 52-year-old man. Although he had pain in his abdomen, insomnia, several diarrheal movements a day and a loss of 40 pounds in weight, he also had symptoms of severe anxiety, vague fears and marked depression. The x-ray findings were repeatedly normal and it was decided to carry out a psychosomatic study.

His mother had died twenty-five years previously, and his father eight years previously. He did not marry early because he was much devoted to his father, and feared that a wife would not take care of the father adequately. As a young man, he went out rarely, and he could not think of marriage because of devotion to his parents. For years he belonged to a gambler's club because it increased his self-esteem, but he did not gamble excessively at any time. After his father's death, when he was 46, he married an attractive widow. She continually nagged him about his habits, and he resented it.

The patient was married for six years to this attractive, aggressive widow. His sex life was exceedingly poor; he could not satisfy his wife. However, he would anticipate with eagerness the one day a week that had been set aside for sexual activity. He claimed that he had for years certain inconsequential habits, but his wife would not allow him to continue them, and this upset him a great deal. He was an extremely jealous person. In addition to his wife, his mother-in-law and two step-daughters occupied the home. The mother-in-law was more nearly the patient's age.

He felt that his wife appreciated him as a provider. His friends and his colleagues thought well of him. He felt insecure in his relations with his wife because he could not satisfy her sexually. Because of this he became abusive with her. His guilt feelings about this abusiveness resulted in numerous crying spells.

He went to the movies occasionally, but had no other kind of entertainment. When he did go to the movies, he often fell asleep during the picture.

His work was very hard. Before his marriage he had owned a hardware store, but had business reverses and lost money. After his marriage, he worked on a delivery truck. He had no difficulties with his superior, and was well liked by his boss and by the other workers.

His attitudes were fixed and inelastic with respect to his old habits, and he thought that the least his wife could do was to cater to his little whims.

During the time of the psychosomatic study, the patient felt better, the diarrhea improved, and during a period of one week he even gained 3 pounds in weight. About two weeks later, when it was felt that the diagnosis was comfortably tucked away in the psychosomatic realm, the clinical picture suddenly changed. The diarrhea, which had partially abated, again increased in intensity. Both legs became markedly edematous. The liver edge could be felt about three fingerbreadths below the costal arch; it was also tender.

At this time, a reconsideration of all the symptoms and signs suggested the diagnosis of carcinoma of the pancreas with metastases to the liver. Laparotomy revealed a hard mass in the region of the body of the pancreas with metastases to the liver. The patient went progressively downhill and died two months later.

The author (11) also had another case which illustrates this point:

A pharmacist, aged 49, complained of a burning feeling in the abdomen, diarrhea, and loss of weight. He was treated by a gastro-enterologist for gastric ulcer, because x-ray examination suggested the possibility of an ulcer niche on the lesser curvature of the stomach. He did not have epigastric pain relieved by food. During a regimen of reassurance and vitamin therapy, his weight remained constant for several weeks. Five months after first being seen, the following letter was received from one of the best known gastro-enterologists in this part of the country.

"I saw this week, Mr. ————, a patient of yours, who walked into this office. He has been complaining for seven months of burning feeling and vague abdominal pain, insomnia and nervousness. He is addicted to the enema and has been a victim of Ménière's disease. I found his physical examination negative. I am sure he is a functional case. I took the privilege of prescribing a sedative for him. I could find no evidence of organic disease."

Following this, he had two months of formal psychoanalysis, and there was some improvement in his condition. One day, I found him sitting on my doorstep, severely jaundiced. A laparotomy revealed carcinoma of the pancreas with metastases to the liver.

Savage and Noble (12) describe 2 additional cases of carcinoma of the pancreas, in both of which psychiatric conditions were diagnosed. Both of these patients exhibited frank psychiatric symptoms, but the organic findings were very questionable. Both were unstable persons and their anxieties were increased by their illness. Savage and Noble believe that certain symptoms distinguish the patients with carcinoma of the pancreas that are seen by the psychiatrist. Characteristically, these patients are in the involutional age group, and the organic findings and localizing signs are minimal. They complain of mild distress after eating, but the description of the pain is vague and unconvincing. There may be loss of appetite and vomiting, and complaints of pain in the back and weight loss. The insomnia seems to be related to the backache. These patients are anxious and depressed and are often beset with feelings of impending doom. The psychopathologic signs are often present in sufficient degree to justify the suspicion of involutional melancholia. Symptoms may be relieved by suggestion and psychotherapy, even in cases of carcinoma of the pancreas; thus, if the patient improves, the diagnostic error is perpetuated. This was the course of events in both patients that Savage and Noble described.

### III. POSSIBLE BIOCHEMICAL ASSOCIATION BETWEEN CANCER AND MENTAL DISEASE

The only known humoral association between cancer and mental disease is that involving a compound having an indole nucleus (serotonin). Even so, this association may be only fortuitous.

A recent case study by Thorson and associates (13) has focused attention on a clinical syndrome associated with metatasizing carcinoid tumors. This condition is characterized by episodes of flushing of the skin resulting in extreme cyanosis, cutaneous telangiectasis, development of a temporary but severe shock-like state, valvular lesions of the right side of the heart, and respiratory distress resembling bronchial asthma. There is often a history of diarrhea, but all x-ray findings are usually normal. A large nodular liver is invariably present. Since large amounts of serotonin (5-hydroxytryptamine) have been found in carcinoid tumors, and in the blood of patients with metastasizing carcinoid tumors, it is logical to assume that the symptoms may be related to an excessive production of serotonin by the tumor.

The development of the chemical concept of psychoses has had a fascinating history. Numerous reports have appeared recently in the medical literature detailing the effect of certain chemical substances on personality. About ten years ago, a Swiss chemist named Hoffman, in the course of preparing a salt of *d*-lysergic acid, noticed that he became restless and dizzy. He went home and found himself in bed in a state of drunkenness, experiencing a visual fantasy of an extraordinarily beautiful series of colors (14). Since then many volunteers have taken this salt, *d*-lysergic acid diethylamide or LSD-25, and have verified the peculiar depersonalizing and hallucinating effects (15). LSD-25 contains the indole grouping. The symptoms experienced closely resemble those of schizophrenia, but they are temporary. Another compound, mescaline, is the active principle of the American Indian plant named peyote. Although not an indole

compound, mescaline also produces symptoms resembling schizophrenia (16). In schizophrenic patients, both LSD-25 and mescaline, in extremely small amounts, have aggravated the mental disorganization. When LSD-25 has been given to neurotic patients, there has been a ventilating of ideas from the unconscious (16).

A search for a common denominator in the various chemical substances that cause changes in personality reveal interesting structural resemblances (Fig. 1). It was suggested by Rinkel and associates (17) that these substances act by interfering with a major enzyme system, probably involving the adrenaline cycle. Hoffer and his co-workers (18) found that 5 chemical substances would produce hallucinations without other effects. These were mescaline, LSD, harmine, ibogaine and hashish (marihuana). The molecular structure of the

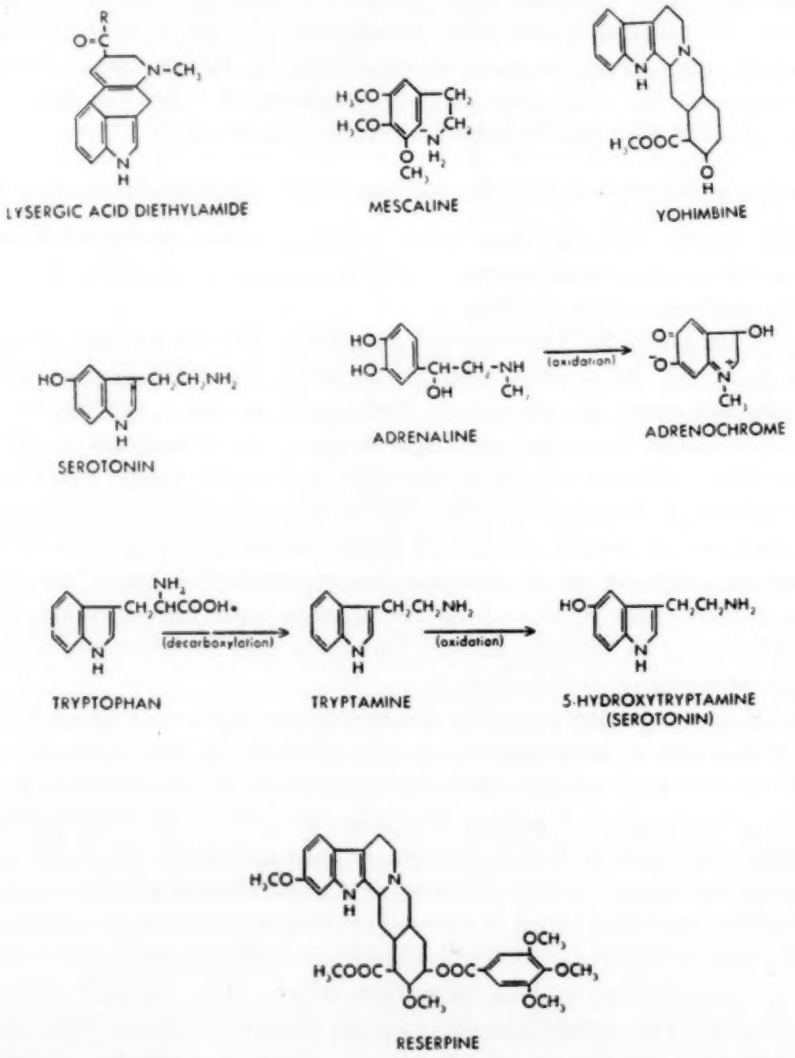


FIG. 1. Chemical substances that cause personality changes. All of these substances have an "indole nucleus," except mescaline, which has an "indole-like nucleus."

first 4 are similar, in that mescaline has an indole-like structure, and the other 3 contain the indole nucleus. One of the patients of Hoffer *et al.* recalled having hallucinatory experiences while taking epinephrine for asthma. Lindemann (19) reported that the symptoms of schizophrenic patients are made worse by epinephrine (adrenaline). Deteriorated adrenaline (which contains adrenochrome) has been known to cause psychologic disturbances (18). Adrenochrome contains the indole nucleus. Adrenochrome has produced psychoses similar to those produced by mescaline (18). Another substance present in the body and containing the indole nucleus is serotonin (20). Serotonin is antagonized by LSD, yohimbine and ergotamine, all of which contain the indole nucleus (21, 22). These substances probably act as metabolic antagonists, in much the same manner as the classic model of sulfonamide versus paramino-benzoic acid. Slater (23) found that serotonin may be a neurohormone and that the pharmacologic properties of LSD may be related to serotonin-mediated activity in the central nervous system. Woolley and Shaw (24, 25) suggested that the mental changes caused by these drugs are the result of the induced deficiency of serotonin in the brain. Thus, they felt that schizophrenics, whose mental symptoms are mimicked by the effects of these drugs, may be suffering from a cerebral serotonin deficiency arising from a metabolic defect.

It is of great theoretical interest that reserpine has an indole nucleus and a chemical structure similar to that of yohimbine. Brodie and his co-workers (26) found that an intravenous injection of reserpine caused a rapid reduction of serotonin in the brain. Within thirty minutes the cerebral serotonin level declined by about 75 per cent, and within four hours by about 90 per cent. The low level persisted for approximately twenty-four hours, and then rose slowly, attaining a normal value after about seven days. Throughout the period of low cerebral serotonin content, 5-hydroxyindole acetic acid (the metabolic product of serotonin) appeared in the urine in appreciable amounts. These authors felt that serotonin was probably still being produced by the body, but was not accumulating in brain tissue.

To complete the circle—it has now been found that reserpine exerts an antileukemic action in mice with this disease (27). A single treatment with reserpine results in a threefold increase in the remaining lifetime of mice with advanced leukemia. Concomitant with the inhibition of local tumor growth by reserpine, there is also diminution of terminal leukocytosis in the peripheral blood.

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# Abstracts of Current Literature

STEROID RESPONSE TO THERAPY IN PROSTATIC CANCER.

Burt, F. B.; Finney, R. P., and Scott, W. W. *J. Urol.* **77:** 485 (March) 1957.

Refined methods have been developed that permit quantitative separation of individual steroid metabolites in unaltered form. They require the use of the enzyme glucuronidase, which has not previously been available to investigators on this subject. The methods of Dobriner and Gallagher were used to study the therapeutic response to steroids and ultimate relapse of patients with prostatic cancer. Two "androgen" metabolites, androsterone and etiocholanolone, and 3 "corticoid" metabolites, 11-hydroxyandrosterone, 11-hydroxyetiocholanolone, and 11-ketoetiocholanolone were isolated and identified by infrared spectrophotometry. The values found for both groups were combined for simplicity. The 17-ketosteroids were measured by a modified Zimmermann reaction. "Androgen" metabolites decreased after castration. "Corticoid" and "androgen" metabolites were found to rise during a relapse of the cancer. This rise paralleled a downhill course. Throughout the studies, the clinical state invariably paralleled the chemical state. Gonadotropin had no effect upon steroid levels in the castrated patients. The effect of ACTH on both "androgen" and "corticoid" metabolites was found to be greatly enhanced by castration. In both intact and castrated patients, stilbestrol caused a fall in "androgen" and "corticoid" metabolites. Cortisone caused a dramatic fall in "androgen" metabolites in a case of relapse following treatment with stilbestrol and castration. Among 10 patients followed for periods of six to seventeen months, 5 progressed satisfactorily and 5 did not. Those who suffered a relapse produced a high percentage of androsterone in relation to physiologically neutral etiocholanolone.

THE EPIDEMIOLOGY OF ATHEROSCLEROSIS AMONG A RANDOM SAMPLE OF CLOTHING WORKERS OF DIFFERENT ETHNIC ORIGINS IN NEW YORK CITY. I. PREVALENCE OF ATHEROSCLEROSIS AND SOME ASSOCIATED CHARACTERISTICS.

Epstein, F. H.; Boas, E. P., and Simpson, R. *J. Chron. Dis.* **5:** 300 (March) 1957.

The prevalence of manifest atherosclerosis and associated conditions was studied among a working population who were members of a Union representing the workers in the men's clothing industry in New York City. Of the total Union population of 33,000 men and women, a sample of 683 men and 592 women aged 40 and over was drawn at random. An additional, nonrandom group of family members, including 183 men and 272 women, was also examined. The majority of the participants belonged to two different ethnic groups, and were first generation immigrants of Italian and Jewish origin. Their social and economic status was otherwise comparable. The prevalence of manifest atherosclerosis in this population was established on the basis of well defined diagnostic criteria. Manifest coronary heart disease was twice as frequent among Jewish as among Italian men but no ethnic difference could be discerned among the women; the sex difference in prevalence was well marked. In contrast, aortic atherosclerosis, diagnosed on the basis of roentgenographic evidence of calcification in the thoracic and abdominal aorta, showed neither an ethnic nor a sex difference. Data on the prevalence of peripheral artery disease and calcifications in the arteries and the prevalence rates for hypertensive and rheumatic heart disease are given. The reported data include information on relative weight, height, and other bodily characteristics, blood pressure and serum lipid levels, the prevalence of diabetes, and the general state of health among this representative population sample and in the two main constituent ethnic groups. Jewish men and women were shown to have higher serum cholesterol levels than their Italian counterparts but serum phospholipid levels were similar in the two ethnic groups. Serum uric acid levels were higher in men than in women but

similar in Italians and Jews. Systolic and diastolic blood pressure levels showed a rise with age but no ethnic difference. No ethnic difference was demonstrated in the prevalence of diabetes mellitus. An analysis of certain insurance records pertaining to this population group confirmed the evidence based on examination of the random population sample that coronary heart disease indeed occurred more commonly among Jewish than Italian men. The study provides an example of a comprehensive epidemiologic study of manifest atherosclerosis and should establish a basis for comparison with other much needed surveys of this kind. (Authors' summary.)

THE EPIDEMIOLOGY OF ATHEROSCLEROSIS AMONG A RANDOM SAMPLE OF CLOTHING WORKERS OF DIFFERENT ETHNIC ORIGINS IN NEW YORK CITY. II. ASSOCIATIONS BETWEEN MANIFEST ATHEROSCLEROSIS, SERUM LIPID LEVELS, BLOOD PRESSURE, OVERWEIGHT, AND SOME OTHER VARIABLES.

Epstein, F. H.; Simpson, R., and Boas, E. P. *J. Chron. Dis.* **5:** 329 (March) 1957.

The prevalence of various manifestations of atherosclerosis was measured among a random sample of clothing workers, aged 40 years and over, of Italian and Jewish extraction, who were comparable with regard to working conditions, socioeconomic status, and dietary intake of calories and fat. The over-all prevalence rate of coronary heart disease among Italian men appeared to be influenced by serum cholesterol, blood pressure, and body weight levels, since the frequency of the disease was consistently greater at higher than at lower levels of these three variables. By contrast, among Jewish men who, as a group, showed evidence of coronary disease more frequently than Italian men, these variables exerted no appreciable effect upon the prevalence of the disease. The sample included too few women with coronary disease for a similar analysis. The prevalence of roentgenographic evidence of aortic calcifications appeared similarly more susceptible to the influence of the three variables in question among Italians than Jews in both sexes. Data relating the prevalence of manifest atherosclerosis to the serum cholesterol-phospholipid ratio and serum uric acid levels are also presented. Aortic calcifications were more commonly seen in the presence than in the absence of manifest coronary disease. Further interrelations between manifest coronary, aortic, and peripheral arterial disease were also made. Comparison of Italian and Jewish men with and without coronary disease in terms of some more obvious possible atherogenic factors failed to delineate a "profile" which might help in characterizing the affected men. These findings indicated primarily that the predisposition to the development of coronary heart disease of Jewish, as compared with Italian, men in this population segment is largely unexplained by any of the factors studied in these investigations. Presently undefined factors appear to be of considerable quantitative importance in determining the prevalence of coronary disease among certain predisposed groups and require further study, particularly by epidemiologic methods. (Authors' summary.)

NOS MOYENS D'ACTION SUR L'HYPERCALCIURIE DES LITHIASES URINAIRES (APPROACH TO HYPERCALCIURIA IN NEPHROLITHIASIS).

Génot, R. *Sem. hôp., Paris* **32:** 2978, 1956; through *Ciba Literature Review* **2:** 51 (Feb.) 1957.

An elevated calcium level in the urine in cases of nephrolithiasis is so often found that its pathogenic effect is no longer in doubt. By attempting to reduce the calcium concentration in the urine, it should be possible to lessen the frequency of relapses. Hypercalciuria should not be considered to exist until, with the patient receiving a normal diet, more than 250 mg. of calcium are excreted in twenty-four hours. An excretion rate of 200 mg., which is usually regarded as the upper limit of the normal range, is found in 25 per cent of healthy subjects. Treatment consists of prescribing a course of mineral waters designed

to increase urinary excretion, the administration of cationic exchange resins which retain calcium in the intestinal tract, or the use of combined androgen-estrogen therapy. These hormones bring about better fixation of calcium in bone tissue. Androgens appear to promote the reabsorption of calcium in the renal tubules. The response is most impressive and quickly apparent, especially in older people. Younger persons, on the other hand, respond less well.

UEBER EINIGE KLINISCHE ASPEKTE DER INTRAVASALEN ERYTHROZYTENBALLUNG (SOME CLINICAL ASPECTS OF INTRAVASCULAR ERYTHROCYTE CLUMPING).

Harders, H. *Schweiz. med. Wchnschr.* **87:** 11, 1957; through *Ciba Literature Review* **2:** 35 (Feb.) 1957.

Sludged blood can be detected in human beings by examining the conjunctival capillaries through the stereomicroscope. This sludged blood cannot be seen in healthy subjects under normal conditions, but may be provoked by cold, reduced oxygen level, or dietetic influences. It also may be observed in many diseases, the prime example being sickle-cell anemia. Marked sludging sets in a few hours after the ingestion of meals rich in fat. This aggregation of red cells, which may possibly be accompanied by intravascular deposits, is reversible at first and cannot from the outset be regarded as genuine thrombosis, although it predisposes to this condition. Changes in the electrocardiographic pattern and feelings of oppression frequently occur even in the healthy subject, and in patients with vascular disorders angina pectoris may develop. Anticoagulants are usually unable either to prevent or to dissolve the sludging, but they can counteract a secondary release of fibrin. Prophylactic measures are important. It is, therefore, advisable to avoid as far as possible giving fatty meals and injecting colloids of high molecular weight before or after operations.

BENIGN TUMORS OF THE LIVER. IV. POLYCYSTIC DISEASE OF SURGICAL SIGNIFICANCE.

Henson, S. W., Jr.; Gray, H. K., and Dockerty, M. B. *Surg., Gynec. & Obst.* **104:** 63 (Jan.) 1957.

Clinical and pathologic observations on 29 patients with histologically proved polycystic disease of the liver are presented. Ten patients had associated polycystic disease of the kidneys, 1 patient had cystic involvement of the spleen, 8 had a history that suggested polycystic disease in other members of their family, 4 had a family history of renal disease, and 2 patients had a family history of hypertension and cerebrovascular accidents. Cysts of the liver are found more frequently in women than in men, the ratio being 4:1 for all types of cysts. In this series the 23 women and 6 men had an average age of 52.8 years, the youngest patient being 34 years old and the oldest 82 years of age. The average normal duration of symptoms was three years. The symptoms usually consisted of a dull, aching pain, a gradually enlarging abdominal mass, or disturbances produced by pressure on adjacent viscera. Other symptoms were dyspepsia, dyspnea, and jaundice. A mass could be palpated in 23 patients. Hepatic function, as measured by values for serum bilirubin and retention of bromsulphalein, was not affected. Other tests of hepatic function gave results within normal limits. Roentgenograms showed a soft-tissue mass in 3 patients, an elevated diaphragm in 3, an extrinsic mass displacing the stomach in 2, and displacement of the right kidney in 1 patient. At operation, the liver was found to be involved with multiple cysts of all sizes. These were thin-walled and contained clear or straw-colored fluid. Histologically the cystic spaces could be seen to be lined with cuboidal or flat epithelium. There was some increase in collagenous connective tissue and mild infiltration with lymphocytes. The disease generally is discovered in persons beyond the age of 40 years. It runs a long and benign course and requires only symptomatic treatment, except in the occasional case in which the contents of large cysts may be aspirated or drained. The 29 patients in the series studied were followed from one to thirty-one years. Hepatic function was found to be impaired in only 2 patients of the group. The patient with hepatic

disease of the liver tended to become adjusted to the increase in the size of his abdomen and by modifying his diet and activities could adapt himself to his limitations. This disease seems to carry less threat to health and life than does polycystic disease of the kidneys, although the latter is consistent with long life.

MASSIVE UPPER GASTROINTESTINAL HEMORRHAGE IN THE UPPER AGE GROUPS. Hoffman, E., and Cohen, E. *Am. Pract. & Digest. Treat.* **8:** 434 (Apr.) 1957.

Fifty-two cases of massive gastrointestinal hemorrhage secondary to duodenal or gastric ulcer were analyzed in order to evaluate the management of patients in the upper age group and to decide whether medical or surgical therapy is indicated. Patients over the age of 50 years were selected for study. Surgery in this series meant operation undertaken at the time of acute hemorrhage. Massive hemorrhage was considered to be one requiring at least 500 cc. of whole blood every six to eight hours in order to maintain the hematocrit at a stable level, or a drop in the hematocrit of at least eight units from a previously known level or from an average normal standard. The findings in these patients over the age of 51 years were as follows: Both duodenal and gastric ulcers were more common in males than in females. For duodenal ulcers with massive hemorrhage treated surgically there was a mortality rate of 23 per cent as compared to a mortality rate of 11.1 per cent for those treated medically. In the case of gastric ulcers, the mortality rates were 13.3 and 50 per cent, respectively. Among the duodenal ulcer patients with massive hemorrhage, 93.5 per cent presented with melena (both red blood and tarry stools), 42 per cent had hematemesis, 42 per cent pain, 6 per cent nausea, and 6 per cent vomiting without the presence of blood. Twenty-nine per cent had had a previous episode of massive hemorrhage. Among the gastric ulcer patients with massive hemorrhage, 72 per cent had melena (including bright red blood and tarry stools), 56 per cent presented with hematemesis and a similar percentage with pain, and 28.5 per cent had had a previous episode of massive hemorrhage. There is a 22 per cent chance of a correct diagnosis in duodenal ulcers, and a 40 per cent chance in gastric ulcer cases, if a gastrointestinal series is carried out during the acute hemorrhage. Operation was the procedure providing the diagnosis in 31 per cent of the duodenal ulcers with massive hemorrhage and in 53 per cent of the gastric ulcers with massive hemorrhage treated surgically. Two cases in this series gave strong support to the idea of a blind gastrectomy when no other source of hemorrhage could be found at the operating table. In one fourth of the cases there was an elevation of the blood urea level, and subsequent return to normal after cessation of bleeding. In cases with massive hemorrhage and transfusions, the van den Bergh reading was elevated in its direct, or its indirect components, or both. In 13 to 16 per cent of the patients receiving large amounts of blood, the hematocrit "boost" phenomenon occurred, the average rise being 5 points. Steel granulomata were observed. In patients in the upper age group with massive hemorrhage from a gastric or duodenal ulcer, large volumes of blood transfusion should be tried. If stabilization of the hematocrit does not occur within a short time (twenty-four to forty-eight hours), the patient should undergo surgery.

INCREASED ERYTHROPOIESIS INDUCED BY ANDROGENIC-HORMONE THERAPY. Kennedy, B. J., and Gilbertsen, A. S. *New England J. Med.* **256:** 719 (Apr. 18) 1957.

The studies on animals and man which show that androgens are involved in erythropoiesis are reviewed. An investigation was undertaken with 68 patients with advanced breast carcinoma treated with androgenic hormones in order better to define this phenomenon. Thirty-two patients received 100 mg. of stanolone (androstanolone, dihydrotestosterone) intramuscularly three times weekly, and 5 received 200 mg. per day orally as methylstanolone. Thirty-one patients received 100 mg. of testosterone propionate intramuscularly three times weekly. Clinical and laboratory manifestations of increased erythropoiesis occurred in 24 patients (35 per cent) within two to eleven months. There was

flushing, heat intolerance, excessive sweating, and dizziness. Plethora and erythema were prominent. Laboratory studies demonstrated an increase in red cell counts, red cell mass, hematocrit, and hemoglobin levels. No alteration occurred in the total white cell or differential count. Platelet counts remained within normal limits throughout the study. There was normoblastic hyperplasia of the bone marrow. The lack of such a response in the remaining 44 patients could not be explained. No correlation could be demonstrated between the tumor response and the increased erythroid activity. The erythropoietic effect was in part dependent upon the dosage and duration of treatment with androgen. It disappeared when the hormone was discontinued. Neither was it maintained during massive cortisone therapy alone. An hypophysectomized woman with breast cancer receiving 75 mg. of cortisone daily demonstrated erythrocytosis only when androgen therapy was begun. The erythroid activity not only rose from low to normal levels but upon prolonged administration of large doses of androgen sometimes increased sufficiently to cause polycythemia. Increased erythroid activity also occurred when testosterone was employed in the treatment of other anemias. There is as yet no explanation of the mechanism of action.

PATHOLOGISCH GESTEIGERTE KÖRNIGE STRÖMUNG IN DEN MICROSKOPISCH SICHTBAREN EPISKLERAL- UND NAGELFALZGEFÄSSEN BEI INNEREN ERKRANKUNGEN (PATHOLOGICALLY INCREASED GRANULAR STREAM IN THE MICROSCOPICALLY VISIBLE EPISCLERAL AND FINGER NAIL VESSELS IN INTERNAL DISEASES).

Liebau, G. *München. med. Wchnschr.* **99:** 11, 1957; through *Ciba Literature Review* **2:** 36 (Feb.) 1957.

Direct microscopic detection of sludged blood in the capillaries of the eyeball or at the base of the finger nails is an important adjunct in the diagnosis of certain internal diseases. This sludging has no connection with the patient's age or sex. The findings in the episcleral vessels agree well with those in the vessels at the base of the finger nails. The results of examinations performed on 320 persons led to the following conclusions: Sludging is never observed in healthy volunteers. When a person is suffering from rheumatoid arthritis or some other disease of rheumatic origin, a distinct sludging is regularly found. It often occurs in cases of jaundice of inflammatory origin, allergic affections (urticaria, eczema, bronchial asthma), or blood diseases. Sludging should be regarded as a nonspecific sign of disease—in the same way as fever or leukocytosis, with which it does not necessarily go hand in hand. In certain instances, however, it assumes importance in differential diagnosis, since in disorders such as sciatica, pleuritis, endocarditis or eczema, it enables the physician to distinguish a rheumatic or allergic etiology from some other pathogenesis.

UEBER CHIRURGISCHE BEHANDLUNG DER ESSENTIELLEN HYPERTONIE (THE SURGICAL TREATMENT OF ESSENTIAL HYPERTENSION).

Nissen, R. *Méd. et hyg.* **14:** 490, 1956; through *Ciba Literature Review* **2:** 55 (Feb.) 1957.

This is a review of extensive experience in the surgical treatment of essential hypertension. Sympathectomy is performed only in cases in which the spastic component of the disease is marked and in which medicinal therapy, as with Rauwolfia, has failed. In almost half of the cases so treated, the operation produces subjective improvement. Cerebral and cardiac complications occur perhaps less frequently, and the patient's life may possibly be prolonged. If, however, the blood pressure levels are examined five years after the operation, the intervention must be acknowledged to have failed in 90 per cent of cases. Nissen is, therefore, skeptical about the value of sympathectomy. He rejects adrenalectomy completely. Of interest is his observation, based on trial excisions of the kidney, that the smallest renal arteries showed endarterial changes in 90 per cent of patients who had undergone sympathectomy, although no renal damage could be detected by function

tests. These changes were also found in patients who, from examination of the eye grounds, appeared to be suffering from the mildest forms of hypertension. On the other hand, it was not possible to show that patients without arteriosclerotic changes must for that reason alone be considered as permanently cured.

SERIOUS HEART DISEASE SIMULATED BY HIATUS HERNIA.

Palmer, E. D. *U. S. Armed Forces M. J.* **8:** 477 (Apr.) 1957.

Patients with direct hiatus hernia may present the symptomatology of coronary artery insufficiency or myocardial infarction. In addition to lack of appreciation of this fact, an important error is made in failure to accept the result of objective studies when they do not confirm the clinical impression of heart disease. It should also be recognized that the pain of hiatus hernia, as well as that of several types of esophageal dyskinesia, responds to the nitrites. For this reason, a therapeutic test of symptomatic response to nitroglycerin in cases thought to be angina pectoris can be misleading. The smaller a hiatus hernia, the more difficult is its diagnosis and the more likely it is to cause severe chest pain. One roentgenographic series showing a normal upper gastro-intestinal tract does not exclude the diagnosis of hiatus hernia. Esophagoscopic examination must also be made before the possibility of hiatus hernia can reasonably be excluded. Among a series of 214 patients with direct hiatus hernia, 7 per cent presented the symptomatology of coronary artery insufficiency or myocardial infarction and were treated for various periods of time as cardiac patients. Case reports are presented for 4 patients. Nine of the patients in the entire group were found actually to have both hiatus hernia and heart disease.

LE DIAGNOSTIC DES INFECTIONS URINAIRES À L'AIDE DE LA RÉACTION DE GRIESS (DIAGNOSIS OF URINARY TRACT INFECTIONS BY MEANS OF THE GRIESS REACTION).

Schaus, R. *Bull. Soc. sc. méd. Luxemburg* No. 3, 83, 1956; through *Ciba Literature Review* **2:** 52 (Feb.) 1957.

The urine of healthy subjects contains a certain amount of nitrates which come primarily from the vegetable components of the diet. The presence of nitrites, on the other hand, always indicates that pathogenic micro-organisms are involved. *Escherichia coli* in particular, but also staphylococci, proteus, and sometimes the typhoid bacillus, have the property of reducing nitrates to nitrites. This property, however, is always absent in streptococci, gonococci, and tubercle bacilli. The detection of nitrites in the urine thus makes it possible to deduce the presence of certain bacteria in the urinary tract without using a microscope or cultures. These nitrites can quickly and easily be detected even by the general practitioner. A small quantity of fresh urine is mixed in a test tube with Griess's reagent in a ratio of 2:1 to 4:1. If nitrites are present, the mixture will soon turn red. Sources of error are rare. The reagent is prepared as follows: 500 mg. of chemically pure sulfanilic acid is dissolved in 150 cc. of 10 per cent acetic acid, and the solution shaken and filtered. A 20-cc. volume of warm distilled water in which 200 mg. of pure *a*-naphthylamine has previously been dissolved, is then added. The solution thus obtained is ready for use immediately and can be stored for several weeks in a dark bottle.

AN EVALUATION OF ENDOCRINE CONTROL THERAPY PLUS RADICAL PERINEAL PROSTATECTOMY IN THE TREATMENT OF SELECTED CASES OF ADVANCED CARCINOMA OF THE PROSTATE FOLLOWED FIVE OR MORE YEARS.

Scott, W. W. *J. Urol.* **77:** 521 (March) 1957.

The results obtained by estrogen therapy plus radical perineal prostatectomy in the treatment of 29 consecutive selected cases of advanced carcinoma of the prostate gland without metastases when first seen are presented and compared with the results from other treatment. After sixty months, 68.9 per cent of the patients were still alive, as com-

pared with 10 per cent in the control group, 29 per cent in a similar series reported in the literature treated with stilbestrol, 31.2 per cent in castration cases, and 43.6 per cent when estrogen and castration were combined. This compares favorably with the 51.3 per cent survival rate among patients in Jewett's series of 78 treated by radical perineal prostatectomy alone. The percentage of deaths not attributable to cancer in the 29 patients in this series was greater than in most of the other groups. The decision as to whether a patient is a suitable candidate for radical surgery is less difficult on the basis of age than from the standpoint of his general physical condition. The combined therapy is not used in any patient beyond 75 years of age. Through careful preoperative and postoperative care, the use of proper supporting measures during operation, and the use of antibiotics, the operation is no more disturbing to the patient than some of the more commonly used surgical procedures on the prostate. Endocrine therapy and radical perineal prostatectomy complement each other well in the treatment of selected cases of advanced carcinoma of the prostate without metastases. In some instances of extraprostatic extension, estrogen therapy makes it possible for extirpation to be carried out at a later date. Postoperative endocrine therapy is necessary to destroy or stem the growth of any small foci of cancer that may be left after surgery. When there is no evidence of extraprostatic extension when the patient is first seen, he should be maintained on estrogen therapy for at least four years postoperatively. The combination of these methods is worthy of further trial. When properly used, the combination will prolong the life of the patient and lengthen the period of his freedom from distressing urinary symptoms.

ERFAHRUNGEN ÜBER RESERPINBEHANDLUNG IN DER GERIATRIE (EXPERIENCE WITH RESERPINE THERAPY IN GERIATRICS).

Seemann, D. *Wien. med. Wchnschr.* **106:** 930, 1956; through *Ciba Literature Review* **2:** 56 (Feb.) 1957.

The tranquilizing and relaxing effect of reserpine makes it possible to apply treatment directed specifically at the autonomic nervous system in excitation states affecting presenile or senile patients. By damping down sympathetic functions, a parasympathicotonic influence is exerted on autonomic nervous reactivity, thus producing a "gentle" parasympathicotonic readjustment. As a result, the stimulus threshold for environmental influences is raised and the reactions to environmental stress factors are reduced. The author treated 56 geriatric patients suffering from various excitation states in which the principal symptoms were affective instability, irritability, insomnia, obsessional impulses, weakness of memory, disordered thinking, reduced critical faculty, and diminished competence associated with a persistent, latent excitation state. Serpasil was administered in doses ranging from 0.1 mg. three times daily to 0.25 mg. six times daily. When the patients revealed symptoms of fatigue, they were given in addition 10 mg. of Ritalin twice daily, which did not lessen the tranquilizing effect of Serpasil. Irrespective of whether the excitation states were the expression of an organic vascular syndrome or whether the clinical picture was dominated by premature signs of decrepitude—in the form of a pseudoneurasthenic condition—the patients were restored to a balanced state of reactivity and their emotional threshold was lowered.

ZOXAZOLAMINE IN GERIATRIC SKELETAL MUSCLE SPASM.

Settel, E. *Am. Pract. & Digest. Treat.* **8:** 443 (March) 1957.

Forty-six patients between the ages of 48 and 87 years who had the common symptoms of voluntary muscle spasm and pain associated with a variety of disease entities received zoxazolamine (Flexin) orally in doses of 500 mg. three to four times daily for an evaluation of the drug's muscle-relaxing properties. The disease entities fell into neurologic, orthopedic and arthritic groups. Diminution of stiffness, increase in range of motion, and reduction of pain were considered the criteria of improvement. The dosage of the drug

was reduced to 250 mg. after maximum improvement was attained or when evidence of side-effects appeared. Zoxazolamine proved to be valuable in the relief of voluntary muscle spasm of spinal or orthopedic origin but less valuable in skeletal muscle spasm of supra-segmental neurologic origin. Improvement occurred more rapidly in acute conditions and after prolonged administration in chronic conditions. The ability of the aged patient to function was increased, so that rehabilitative activities could be undertaken. Side-effects, which included fatigue, drowsiness, tremor, vertigo, rash, mild laryngeal edema, nausea and weakness occurred in 9 (19 per cent) of the patients and were sufficiently intense to cause withdrawal of the drug in 3 (6 per cent). All side-effects were readily reversible. Nausea in 2 cases was relieved with chlorpromazine. No evidence of hepatic, renal, or bone-marrow injury could be detected during the administration of the drug.

"MOOD" THERAPY IN THE AGED. DIFFERENTIAL APPROACHES TO RECENT THERAPY. Smigel, J. O. *Med. Times*, (New York) **85:** 149 (Feb.) 1957.

The approach to therapy of elderly people when elements of anxiety, fear, disorientation, agitation, confusion or depression are present is discussed and the need for individualization of therapy stressed. Whereas the elderly may have learned to live with physical ailments, the reverse is true of emotional states and they loom larger than ever. Three hundred and fifty-five elderly patients were observed for the ability of Metrazol, reserpine, chlorpromazine, promazine, the meprobamates in sequence, and Atarax to alter moods and emotional states. These patients were studied and evaluated during the course of four years, but in no case for less than three months. Metrazol proved to be the standby for most senility symptoms when hypertensive factors were secondary, and as follow-up therapy after reserpine or chlorpromazine. Although its effect takes place slowly, it acts with increasing effectiveness and a greater degree of permanence in mood control than the presently known tranquilizers. Reserpine was used chiefly when hypertension was present, and chlorpromazine when hypertension was not the chief complaint. Either of these two drugs in combination with Metrazol permitted earlier substitution of Metrazol alone and lessened the danger of toxic manifestations observed with these drugs used singly. Chlorpromazine enhanced the action of reserpine, but could be combined with Metrazol with greater effectiveness and safety than reserpine. Chlorpromazine alone produced marked jaundice in 2 patients. Promazine did not prove to be a satisfactory substitute for chlorpromazine, so the latter was continued with greater care in determining the individual dosage. This also eliminated drowsiness which had been encountered in 1 patient. In the hypertensive patient, reserpine proved of greatest value in altering anxiety and fear and was also valuable in normotensive patients. However, with time, it lost its potency in these respects as well as its hypotensive effect in elderly patients. Chlorpromazine also proved of great value in altering anxiety and other senility states. Its potential towards side-effects and its tendency to increase the shallowness of shallow respirations in the aged limited its value in milder anxiety states. In patients bordering upon the psychotic, its value surpassed that of other tranquilizers. Meprobamates were used in 32 patients whose average age was slightly above 74 years. Eight had had no previous medication for the conditions under observation, 20 had received a tranquilizer, and 4 had received cerebral stimulants. The meprobamates had a marked effect on fear as distinguished from anxiety. The period of maximum benefit in altering anxiety states and in sleep-producing effect was shorter than from chlorpromazine or reserpine. They had the property of renewal of effect after a rest. Although these drugs could be continued indefinitely, they did not remain effective indefinitely. They caused such minor side-effects as gastric distress, drowsiness, and skin irritation. Among 123 patients receiving Metrazol initially, 42 were hypertensive and 81 were normotensive or hypotensive. Anxiety was predominant in 62 of them. Metrazol controlled anxiety without hypertension, alone or accompanied by either agitation or depression. Patients who were depressed or who showed only anxiety symptoms responded more readily than agitated patients. When anxiety predominated and other symptoms were minor, the meprobamates were chosen for initial therapy. However, when a long-continued effect was required, Metrazol was used instead. Metrazol

also was used in cases of disorientation and confusion. The meprobamates have no marked effect upon these symptoms. The Rauwolfia preparations have a positive effect upon these symptoms, particularly when hypertension is an etiologic factor and cerebral arteriosclerotic changes are dominant. The author concludes that most of the tranquilizers have realistic values in anxiety states. In prescribing, the physician must take into account environmental, situational, social, and societal factors as well as somatic and psychologic ones. Tranquilizers should not be prescribed without restriction, nor at the discretion of the patient. It should be remembered that measures other than tranquilizers may afford more permanent results and with less danger to the patient.

PAIN IN THE LOWER LIMB AFTER SYMPATHECTOMY.

Tracy, G. D., and Cockett, F. B. *Lancet* **1:** 12, 1957; through *Ciba Literature Review* **2:** 53 (Feb.) 1957.

Lumbar sympathectomy is followed by typical pain in about 18 per cent of cases. After a latent period of ten to seventeen days, severe and unremitting pain suddenly makes itself felt. It is worst at night and always affects the same area, that is, the anterior parts of the thigh down to the knee. The pain, always associated with marked hyperesthesia, proves so persistent that some patients have sleepless nights for weeks on end. A gradual, spontaneous remission frequently takes place after ten to sixteen weeks, but in some cases the pain may last for months. This syndrome seems to be peculiar to the operation of sympathectomy, since it is not seen after other operations in which somatic nerves may be injured. The skin of the affected area is cool and moist, and its sensory properties are maintained. There are signs of a substantially increased sympathetic activity. By measuring the electrical resistance of the skin, it was observed, for instance, that the sweat glands in the affected area were in a state of increased activity. This hyperactivity is probably due to the presence of accessory sympathetic ganglia.

INFLUENCE DE LA RÉSERPINE SUR LES GLANDES ENDOCRINE (INFLUENCE OF RESERPINE ON THE ENDOCRINE GLANDS).

Tuchmann-Duplessis, H. *Presse méd.* **64:** 2189, 1956; through *Ciba Literature Review* **2:** 60 (Feb.) 1957.

Clinical and experimental observations make it appear probable that the site of attack of the centrally acting component of Serpasil is the hypothalamus, that is, a part of the brain which controls the activity of the pituitary. The author was able to show in animal experiments that Serpasil provokes histologic changes in the pituitary. For instance, the number of large basophilic cells decreased and a change took place in the ratio of small to large basophils. These anatomic findings agree with the observation that the normal balance between the follicle-stimulating hormone and the luteinizing pituitary hormone is disturbed, the FSH decreasing and the LH increasing. The excessive supply of luteinizing hormone could account for various changes in the male and female genital organs (regressive changes in the ovaries and—despite maintenance of spermatogenesis—in the interstitial testicular tissue; suppression of estrus). In about a third of cases, Serpasil affects the thyroid gland as well by slowing down its function. This has also been observed clinically in patients with hyperthyroidism. In addition, Serpasil appears in many cases to stimulate the adrenal cortex—an effect which is indicated by hyperemia and hypertrophy of the organ as well as by histologic changes.

USE OF ANTEROPUBIC FASCIAL SLING FOR TREATMENT OF SURGICAL INCONTINENCE IN THE MALE.

Uhle, C. A. W. *J. Urol.* **77:** 478 (March) 1957.

This is a summary of experience with a fascial sling placed anterior to the pubis and above the bulbous urethra for the control of urinary incontinence in the male. Among

the 8 cases reported, the aponeurosis of the rectus muscle was used in 5, the fascia lata of the thigh in 2, and both in the eighth case. The ages of 6 of the patients were between 50 and 80 years. Partially satisfactory results were obtained in 4 patients. They could start and stop the urinary stream at will. Dribbling occurred at times of stress. This operation is not undertaken until sufficient time has elapsed to establish that incontinence is permanent and irrevocable. It must be preceded by corrective surgery for any pathologic deviations found within the bladder and urethra that may have a causal relationship to the incontinence. The sling operation should be reserved for incontinence following operations on an obstructive prostate gland or that following trauma to the urethra. The technic is discussed. Errors in the preparation of the strips of fascia, namely, making them too short for proper adjustment or having them tear, can account for failure. An indwelling catheter should always be inserted at the conclusion of the operation. The operation is based upon the concept that the creation of an artificial sphincter about the bulbous urethra would aid in the control of urine in several ways: 1) tension on the abdominal wall would compress the sling against the bulbous urethra; 2) the perineal body containing the external sphincter mechanism would be elevated and strengthened; and 3) urinary flow would be decreased by compression of the bulbous area of the urethra against the urogenital diaphragm. The author believes that failure in half of the patients and not completely satisfactory results in the remainder in this series may have been due to lack of fulfillment of these postulates with the anteropubic course of the sling. The fascial sling is not a physiologic process. Since the validity and usefulness of a surgical technic for the correction of urinary incontinence depend upon the maintenance of principles of physiologic integrity, the author concludes that further study of the procedure and analysis of cases is required.

TREATMENT OF CHRONIC GRANULOCYTIC LEUKEMIA WITH MYLERAN.

Unugur, A.; Schulman, E., and Dameshek, W. *New England J. Med.* **256:** 727 (Apr. 18) 1957.

Myleran (1:4-dimethanesulfonyloxybutane) was used in the treatment of 35 patients with chronic granulocytic leukemia. The initial dosage of the drug was 8 to 16 mg. daily for one or two weeks. The maintenance dosage was 1 or 2 mg. daily. All patients experienced alleviation of symptoms, restoration of normal blood values, and some regression of the spleen within the first two months of therapy. Complete clinical and hematologic remissions occurred in almost every case and were maintained by small daily dosages. In some cases in which leukopenia developed, sustained remissions for eighteen to twenty months or more were obtained. A terminal myeloblast crisis developed in 6 patients, six to twenty-three months after therapy was begun. Experience with previous therapeutic agents in chronic granulocytic leukemia indicates that myeloblast crisis occurs in the majority of the cases as a terminal event, one to three years after institution of therapy. The simplicity of administration of Myleran, its relative freedom from side-effects, and its consistency of effect are important advantages as compared with radiation therapy. The consistency of the effects of Myleran and its apparent specificity for the treatment of one kind of leukemia lead to a degree of optimism for the eventual control of various forms of leukemia. (From authors' summary and conclusions.)

CLINICAL STUDY OF PROCLORPERAZINE, A NEW TRANQUILIZER FOR THE TREATMENT OF NONHOSPITALIZED PSYCHONEUROTIC PATIENTS.

Vischer, T. J. *New England J. Med.* **256:** 26 (Jan. 3) 1957.

Thirty-eight patients (11 males and 27 females), of average age 57.5 years and representative of patients seen by the practicing physician, were treated with proclorperazine (Compazine), a recently developed analog of chlorpromazine. Among these patients, 16 had primary vascular disease (hypertension, arteriosclerotic heart disease, cerebrovascular

accidents, or thrombotic episodes). Some of the others had migraine headaches, alcoholism, rheumatoid arthritis, or involutional melancholia. A psychoneurotic element was present in all of the patients and had made treatment difficult. Among them were some cases of involutional and senile depression. These patients complained chronically of headaches, vertigo, visual disturbances, palpitation, profuse sweating, anorexia, and minor gastrointestinal disturbances. The dosage usually was 5 mg. of proclorperazine three or four times daily. Treatment was carried on for four to eight or ten weeks. Proclorperazine was tested for its effect when psychoneurotic symptoms including anxiety, depression, nervousness, confusion, tension, and emotional instability were present. After treatment 21 patients became free of symptoms and achieved a response better than that to other medications. Confusion and depression disappeared. The patients became more relaxed, less nervous, and less tense; they returned to work or acquired a new interest in their surroundings. Sixteen patients were partially relieved. One patient with involutional melancholia of twelve years' duration improved only slightly. Mild but transient drowsiness occurred in 5 patients. The use of large doses of sedatives proved unnecessary during the administration of proclorperazine. The drug was concluded to be highly effective for the treatment of patients with psychic stress alone or accompanied by physical complaints.

BASAL CELL EPITHELIOMA AND BASALOID LESIONS OF THE ANUS.

Wittoesch, J. H.; Woolner, L. B., and Jackman, R. J. *Surg., Gynec. & Obst.* **104:** 75 (Jan.) 1957.

A study was made of 28 anal tumors that showed basal-cell features. Seven were basaloid small-cell carcinomas (Group I) that occurred near the dentate line and were highly malignant. The duration of symptoms in patients with this kind of tumor was short. Complaints in the other groups had usually been present for several years. The other groups consisted of 9 basaloid squamous-cell epitheliomas (II), 10 true basal-cell epitheliomas (III), 1 papillary squamous-cell epithelioma (IV), and 1 adnexal tumor (V). All behaved like corresponding lesions of the skin. The adnexal tumor was benign. The basal-cell epitheliomas occurred predominantly in the anal margin. The basaloid squamous-cell epitheliomas were scattered throughout the anal canal. The sex distribution was equal, except that in Group III, 9 of the 10 patients were men. The patients in all groups were in their late fifties or early sixties. They were treated by local excision, or radical operation with or without radiation therapy. A few received radiation therapy only. In Group I, 1 untreated patient survived for one year. Only 1 patient of this group was alive and well seven months postoperatively. Two Group II patients remained alive at eight and thirteen years, respectively, following local excision. Another in this group died fifteen years following local excision. Two other patients died at three and eight years postoperatively, and another died ten days after operation from coronary heart disease. Nine of the 10 patients in Group III were treated by local excision, with radium therapy in 3. Six remained alive and well for periods of three to thirteen years. One died after four years, from carcinoma of the prostate. One patient in this group refused treatment. The patient with the adnexal tumor remained alive and well two years following local excision and radiation therapy. All patients not otherwise accounted for were lost to follow-up. It is suggested that some of the metastasizing basal-cell epitheliomas and basosquamous epitheliomas of the anal canal reported in the literature actually have been lesions of the type represented by basaloid small-cell carcinomas. It is important to distinguish these latter highly malignant lesions from basal-cell epitheliomas and from squamous-cell epitheliomas simulating basal-cell epitheliomas.

# NEWS AND NOTICES

## NEW FILM IN A.M.A. SERIES ADVISES DOCTORS HOW TO AVOID PROFESSIONAL LIABILITY HAZARDS

A new film that shows physicians how to avoid the recurrent headache of medical practice today—the professional liability claim—is now available from the American Medical Association film library for county society and other professional bookings.

Titled "The Doctor Defendant," the new film was given its first showing this week (June 5) in the New York Coliseum before a large audience of physicians attending the 106th annual meeting of the A.M.A. The 34-minute black-and-white sound film is the second in the "Medicine and the Law" film series produced by the Wm. S. Merrell Company, ethical pharmaceutical laboratories of Cincinnati, Ohio, in cooperation with the A.M.A. and the American Bar Association.

The new movie presents in concise and dramatic terms the stories of four doctors who find themselves cast in the disturbing role of "The Doctor Defendant." In reviewing these cases, the film also demonstrates how a county medical society professional liability review committee functions.

Medical societies may book "The Doctor Defendant" from the A.M.A. film library beginning July 1 for showings before their own members. "The Doctor Defendant" is a companion film to "The Medical Witness" which depicts right and wrong methods of presenting medical testimony by re-enacting a personal injury trial. Both films can be booked together as part of a legal medicine seminar.

Produced as a service to the medical and legal professions, "The Doctor Defendant" presents four cases which are among the most frequently encountered and most representative of what the physician has to face.

The first case is that of a physician charged with negligence in causing a burn during x-ray therapy. In another case the doctor is sued because a doctor unthinkingly criticizes the way an orthopedic patient has been treated. In the third, a claim of unnecessary surgery is made, and in the last case a physician is sued when he advises his patient by telephone and an unfortunate result occurs.

All are common situations; however, they are situations about which the physician is generally poorly informed. "The Doctor Defendant" dramatically explains the legal basis on which these suits are brought, and the areas in which the physician is vulnerable. It shows the best methods to avoid involvement and offers concrete advice on how the physician should handle himself once he has been made the target of a professional liability claim.

Special reference is made to the professional liability review committees that have been set up by some of the county medical societies. The film shows one of these committees in action and how it serves the public and the physician member who is in trouble.

Here are seven suggestions for the practicing physician who wishes to avoid liability involvement, as illustrated by "The Doctor Defendant":

1. Explain to the patient the proposed course of therapy and advise him when treatment may be hazardous.

2. Confirm in a letter to the patient the effect of treatment when harmful side-actions or results might be expected. Obtain written consent for operative procedures. *Remember to keep a copy for your file.*

3. Review and interpret the clinical significance of all diagnostic or laboratory tests *before* a surgical procedure.

4. A precipitating cause of a large number of professional liability actions is the unthinking comment of a physician or treatment given a patient by another physician. All the facts may not be known. . . .so avoid tactless comment.

5. Always remember the protective value of a complete case record. It has been shown again and again that the doctor's best defensive tool in a professional liability claim or suit is the detailed case record.

6. All professional liability claims should be reported promptly to the proper persons; this may save time and unnecessary legal involvement.

7. Be constantly aware of the physician's responsibility to the patient. It is the physician alone who must decide the medical care to be provided.

Societies desiring to show "The Doctor Defendant" and/or "The Medical Witness" may write to the Film Library, American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois, or to Dr. John B. Chewning, director of professional relations, The Wm. S. Merrell Company, Cincinnati 15, Ohio.